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CJS

# The Canadian Journal of Surgery
# Le journal canadien de chirurgie

Vol. 31, No. 6, November 1988 Novembre

- Soft-Tissue Sarcomas
- Peritoneovenous Shunts
- Incidental Appendectomy

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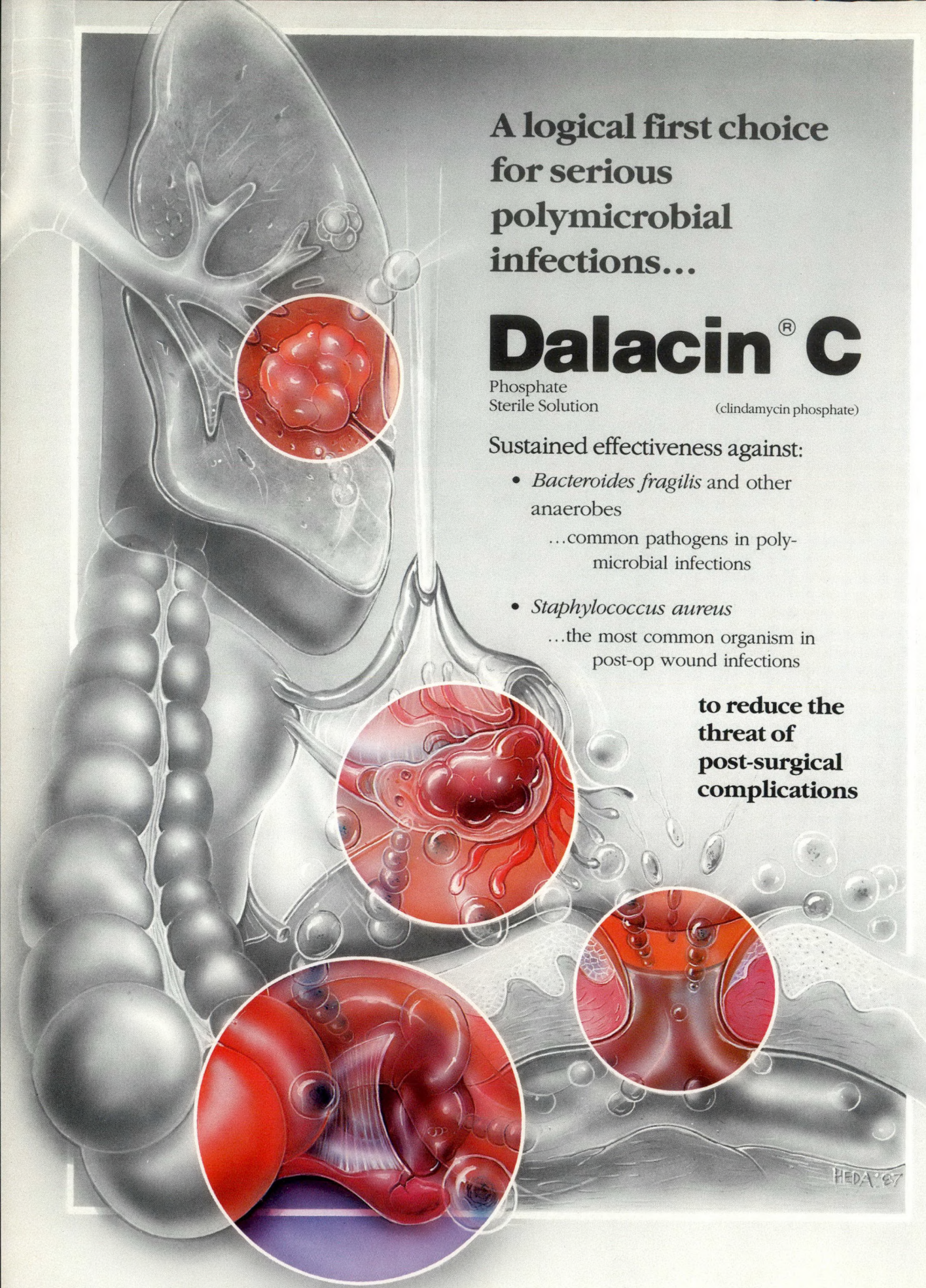


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CJS

# The Canadian Journal of Surgery
# Le journal canadien de chirurgie

Vol. 31, No. 6, November 1988 Novembre
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**Cover picture**

Nickels and magnets — a mass swallowed deliberately to alleviate epigastric discomfort (see page 413)

# Diabetes and the Surgeon

D. Michael Grace, MD, FACS, FRCSC

*Member, Editorial Board, Canadian Journal of Surgery. Associate Professor of Surgery, University of Western Ontario, University Hospital, London, Ont.*

In this issue (pages 421 to 426), Warnock and colleagues describe a technique of pancreatic islet isolation, purification and implantation which can produce normoglycemia in dogs for prolonged periods. This work is important because it hastens that day when successful islet transplantation may be used to fight the devastating long-term effects of insulin-dependent diabetes mellitus.

Diabetes mellitus of both types is a common problem in both medical and surgical patients. Efforts to control blood sugar levels may complicate routine surgical procedures, and infection or emergency operation makes management of the diabetic even more difficult. Abdominal pain may be difficult to assess in a patient with ketoacidosis. Surgeons may also be called to treat complications of diabetes, such as foot infection or ulceration resulting from diabetic vascular disease or neuropathy. In spite of aggressive conservative treatment, diabetes and its associated complications are the most common cause of nontraumatic limb amputation. Diabetic renal disease is now a common cause of chronic renal failure. In such patients, it is a challenge to establish an arteriovenous fistula or graft for hemodialysis because the rate of atherosclerosis is accelerated and the arterial wall is of poor quality. Renal transplantation carried out by surgeons for end-stage renal failure in diabetes can present a moral and technical dilemma. The results are improving, but chronic immunosuppression can further complicate the management of a "brittle" diabetic. Diabetes is also the most common cause of blindness in Canada and ophthalmologists must often treat retinal disease and cataracts in diabetics. Non-insulin-dependent diabetes mellitus occurs later in life but may produce similar complications. The role of gastroplasty in the treatment of morbid obesity remains controversial, but there is no doubt that substantial weight loss in obese

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*Detailed instructions to contributors, in English and French, appear on page 69 of the January 1988 issue.*

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diabetics corrects the condition and may reduce the frequency and severity of subsequent problems.

The prevention of complications in insulin-dependent diabetics remains insoluble in spite of worldwide research efforts. Genetic counselling may prevent some cases, and better understanding of the immunologic causes of diabetes may help to prevent the disease or result in the early treatment of others. Recognition of the autoimmune nature of diabetes mellitus in rats led to the demonstration that cyclosporine could prevent the disease.[1] Trials of cyclosporine in insulin-dependent diabetics have demonstrated that the condition may be prevented or severity reduced if cyclosporine is started early.[2] However, the number of children who can be treated is small and treatment is expensive. Moreover, it remains to be proven whether the complications are indeed prevented. Cyclosporine carries its own set of complications, including renal damage, which may be nearly as serious as the nephropathy one is trying to prevent. Tight control of blood sugar levels by regular insulin injection or use of insulin pumps has resulted in an increased number of hypoglycemic reactions but has not decreased the retinopathy, nephropathy, neuropathy or peripheral vascular disease. A national trial is attempting to answer this question with certainty.[3]

To surgeons, transplantation of the whole pancreas has usually made more sense than it has to endocrinologists. Our emphasis has been on improved techniques, graft survival and freedom from insulin requirement when we should be striving for normal metabolism and freedom from diabetic complications. We were also encouraged by the success of other transplants. Renal transplantation proved more effective in humans than in animals, it improved the quality of life and saved money. Liver and heart transplants were dramatic, effective and lifesaving. The technical problems of pancreatic transplantation are no more challenging than those of renal transplantation, although management of the pancreatic duct has been controversial. When the pancreatic duct was drained to the peritoneal cavity, pancreatic ascites resulted and gave way to enteric anastomosis or occlusion of the duct with polymers. Now drainage of the duct to bladder has achieved better results and has allowed closer monitoring of rejection by measurement of urinary amylase levels. Surgeons familiar with the potential for pancreatitis or pancreatic cysts, abscesses or fistulas after pancreatic surgery have respect for this organ and the potential complications of transplantation. The results in transplantation of the pancreas have improved so that, currently, an average of 50% of grafts are functioning after 1 year and most patients survive.[4] Between 1966 and March 1988, 1394 pancreatic transplants were reported to the Pancreas Transplant Registry at the University of Minnesota.[4] Results have improved steadily due to better immunosuppression and surgical techniques.

The questions that have not been answered include the appropriate indications for transplantation of the pancreas, the timing of the procedure and its effect on the complications of diabetes. Transplantation of the pancreas early in the course of diabetes in rats can prevent nephropathy.[5] Therefore, pancreatic transplantation carried out early in the course of human diabetes makes sense; however, not all diabetics have complications, and the long-term risks of immunosuppression and rejection are substantial. It, therefore, makes more sense to transplant the pancreas in diabetics with renal failure who receive a renal transplant and are already on immunosuppression. Simultaneous renal and pancreatic transplantations appear not to harm the kidney and may result in better pancreatic survival.[4] Unfortunately, transplantation may not reverse diabetic complications.[6,7] It is not surprising that severe retinopathy, neuropathy or nephropathy do not improve with normoglycemia. Although pancreatic transplantation should continue to be evaluated as part of research protocols, it is difficult to recommend its widespread use until immunosuppression is free of side effects and it is clear that the complications of diabetes can be prevented or delayed.

Because many of the technical complications of pancreatic transplantation are due to unnecessary exocrine tissue, transplantation of pancreatic islets has always been more attractive. The dilemma is that isolation techniques are especially difficult in larger animals, that prolonged function of transplanted islets is poor and that islets seem more susceptible to rejection than whole pancreas. The best route of injection has not been established with certainty, although portal injection via the umbilical vein is easiest in humans. Vascular complications in animals can be prevented by islet transplantation,[8] but islets appear not to function as well or as long as whole pancreas, even when rejection is not a factor.[5] New techniques for decreasing pancreatic islet immunogenicity include prolonged culture at 24°C,[9] use of multiple donors[10] and treatment of islets with ultraviolet irradiation.[11] Fetal islets from multiple donors have been used in China with limited success,[12] but there are ethical barriers to the use of such techniques in North America. Transplantation of islets encapsulated in a membrane that prevents rejection

but allows diffusion of insulin is an exciting technique developed in Canada.[13] This method has proven effective in rodents, but fibrosis around the capsules may limit its long-term effectiveness in larger animals.

Isolation and purification of sufficient numbers of islets from one donor to maintain blood sugar levels in a recipient increases the chances of successful transplantation in humans. This would be even more likely if improved isolation techniques could be combined with methods to decrease islet immunogenicity. Unfortunately, destruction of transplanted islets by autoimmune reaction rather than rejection is still a risk. Studies on the prevention of diabetes by immunosuppression and on the relation between control of diabetes and its complications must continue. Canadian centres should perform and closely evaluate transplants of whole pancreas and follow with interest the results achieved around the world and reported regularly by the Pancreas Transplant Registry at the University of Minnesota. However, islet transplantation may be the best hope for treating insulin-dependent diabetes mellitus, so Canadian surgeons must continue to follow and contribute to this work.

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# Dalacin® C Phosphate Sterile Solution

(clindamycin phosphate)

## Antibiotic

### Recommended Applications

**Action:** Clindamycin exerts its antibacterial effect by causing cessation of protein synthesis and also by causing a reduction in the rate of synthesis of nucleic acids.

**Indications:** Dalacin C Phosphate (clindamycin phosphate) is indicated for the treatment of infections where the oral route is not indicated or feasible.

Dalacin C Phosphate is indicated in the treatment of serious infections due to sensitive anaerobic bacteria, such as Bacteroides species, peptostreptococcus, anaerobic streptococci, Clostridium species and micro-aerophilic streptococci.

Dalacin C Phosphate is also indicated in serious infections due to sensitive Gram-positive organisms (staphylococci, including penicillinase-producing staphylococci, streptococci and pneumococci) when the patient is intolerant of, or the organism resistant to other appropriate antibiotics.

**Contraindications:** The use of Dalacin C Phosphate (clindamycin phosphate) is contraindicated in patients previously found to be hypersensitive to this compound, the parent compound, clindamycin, or clindamycin palmitate. Although cross-sensitization with Lincocin® (lincomycin hydrochloride) has not been demonstrated, it is recommended that Dalacin C Phosphate not be used in patients who have demonstrated lincomycin sensitivity.

Until further clinical experience is obtained, Dalacin C Phosphate is not indicated in the newborn (infants below 30 days of age), or in pregnant women.

**Warnings:** Some cases of severe and persistent diarrhea have been reported during or after therapy with Dalacin C Phosphate (clindamycin phosphate). This diarrhea has been occasionally associated with blood and mucus in the stools and has at times resulted in acute colitis. When endoscopy has been performed, some of these cases have shown pseudomembrane formation.

If significant diarrhea occurs during therapy, this drug should be discontinued or, if necessary, continued only with close observation. Significant diarrhea occuring up to several weeks post-therapy should be managed as if antibiotic-associated.

If colitis is suspected, endoscopy is recommended. Mild cases showing minimal mucosal changes may respond to simple drug discontinuance. Moderate to severe cases, including those showing ulceration or pseudomembrane formation, should be managed with fluid, electrolyte, and protein supplementation as indicated. Corticoid retention enemas and systemic corticoids may be of help in persistent cases. Anticholinergics and antiperistaltic agents may worsen the condition. Other causes of colitis should be considered.

Studies indicate a toxin(s) produced by Clostridia (especially Clostridium difficile) may be a principal cause of clindamycin and other antibiotic-associated colitis. These studies also indicate that this toxigenic Clostridium is usually sensitive *in-vitro* to vancomycin. When 125 mg to 500 mg of vancomycin were administered *orally* four times a day for 5 - 10 or more days, there was a rapid observed disappearance of the toxin from faecal samples and a coincidental recovery from the diarrhea.

It should be noted that serious relapses have occurred up to one month after apparently successful treatment. A relatively prolonged period of continuing observation is therefore recommended.

**Precautions:** Dalacin C Phosphate (clindamycin phosphate), like any drug, should be prescribed with caution in atopic individuals. Dalacin C Phosphate must be diluted for intravenous administration. (See Dosage and Administration)

The use of antibiotics occasionally results in overgrowth of nonsusceptible organisms - particularly yeasts. Should superinfections occur, appropriate measures should be taken as dictated by the clinical situation.

As with all antibiotics, perform culture and sensitivity studies in conjunction with drug therapy.

Since abnormalities of liver function tests have been noted occasionally in animals and man, periodic liver function tests should be performed during prolonged therapy. Blood counts should also be monitored, during extended therapy.

Dalacin C Phosphate may be used in anuretic patients. Since the serum half-life of clindamycin in patients with impaired hepatic function is greater than that found in normal patients, the dose of Dalacin C Phosphate should be appropriately decreased. Hemodialysis and peritoneal dialysis are not effective means of removing the compound from the blood. Periodic serum levels should be determined in patients with severe hepatic and renal insufficiency.

**Adverse Reactions:** ***Local***

(a) *Intramuscular Injections:* Of 404 patients treated with Dalacin C Phosphate (clindamycin phosphate) intramuscularly (with a solution containing 150 mg/ml), six (1.5%) demonstrated local reactions as follows: Two complained of pain at the injection site, two demonstrated induration at the injection site and two developed sterile absesses.

(b) *Intravenous Infusions:* Of 192 patients treated with Dalacin C Phosphate by intravenous infusion, 14 (7.3%) demonstrated local reactions. Eleven patients developed superficial thrombophlebitis and one patient developed both superficial and deep thrombophlebitis. The majority of these cases developed in conjuction with the use of indwelling I.V. catheters and it is difficult to know how much the drug contributed to the irritation. Two patients developed localized erythema, swelling and pain at the site of the infusion.

**Systemic Side Effects:** Twenty-eight patients of 596 treated with Dalacin C Phosphate (clindamycin phosphate) by either the intramuscular or intravenous routes developed systemic side effects as follows:

| | *Number of Patients* |
|---|---|
| Rash | 7 |
| Urticaria | 1 |
| Pruritus | 1 |
| Fever, Leucocytosis | 1 |
| Nausea, with or without vomiting | 1 |
| Diarrhea (See also under "Warnings") | 4 |
| Hypotension | 1 |
| Hypertension | 1 |
| Shortness of Breath | 1 |
| Superinfection* | 4 |
| Cardiac arrest** | 1 |
| Bad or bitter taste in mouth | 5 |

* Superinfection is a complication of antibiotic therapy in general and is not necessarily a true side effect of clindamycin phosphate.

** Due to underlying myocarditis in this patient.

**Clinical and Laboratory Findings:** Patients treated during clinical trials of Dalacin C Phosphate (clindamycin phosphate) were followed with clinical laboratory tests, including complete hematology, urinalysis and liver and kidney function tests. Some of these tests were abnormal initially and returned to normal during therapy with Dalacin C Phosphate, while others were normal initially and became abnormal, during therapy. Overall evaluation of clinical laboratory values in these patients does not indicate that Dalacin C Phosphate therapy has a toxic effect on the hematopoietic, hepatic or renal systems. Transient elevations of serum transaminases have occured in some patients, but other liver function tests (alkaline phosphatase, serum bilirubin) have not shown any tendency to increase and there have not been clinical signs of drug-induced hepatic toxicity.

**Symptoms and Treatment of Overdosage:** No cases of overdosage have been reported. No specific antidote is known. Doses as high as 1200 mg every six hours (4800 mg/day) by infusion for five days have been given without adverse effects.

### DOSAGE AND ADMINISTRATION

**Adults**

**Intramuscular Injection:** 600 mg/day in 2 equal doses.
*Moderately severe infections:* 600 to 1200 mg/day in 2 or 3 equal doses.
*Severe infections:* 1200 to 2400 mg/day in 2, 3 or 4 equal doses. Intramuscular injections of more than 600 mg into a single site are not recommended.

**Intravenous Administration:** Dalacin C Phosphate (clindamycin phosphate) must be diluted prior to I.V. administration to a dilution of 300 mg in 50 mL of diluent (6mg/mL) or more, and infused in not less than 10 minutes. Administration of more than 1200 mg in a single 1 hour infusion is not recommended. Dalacin C Phosphate should not be injected intravenously undiluted as a bolus.

*Moderately severe infections:* 900 to 1800 mg/day by continuous drip or in 2 or 3 equal doses, each infused over 20 minutes or longer.

*Severe Infections:* 1800 to 2700 mg/day by continuous drip or in 3 or 4 equal doses, each infused over 20 minutes or longer. In life-threatening infections, doses of 2700 to 4800 mg/day by continuous drip or in 3 or 4 equal doses each infused over 20 minutes or longer may be given.

**Dilution and infusion rates:**

| *Dose* | *Diluent* | *Time* |
|---|---|---|
| 300 mg | 50 mL | 10 min. |
| 600 mg | 100 mL | 20 min. |
| 900 mg | 150 mL | 30 min. |
| 1200 mg | 200 mL | 45 min. |

Alternatively, drug may be administered in the form of a single rapid infusion of the first dose followed by continuous I.V. infusion as follows:

| *To maintain serum clindamycin levels* | *Rapid infusion rate* | *Maintenance infusion rate* |
|---|---|---|
| Above 4 mcg/mL | 10 mg/min. for 30 min. | 0.75 mg/min. |
| Above 5 mcg/mL | 15 mg/min. for 30 min. | 1.00 mg/min. |
| Above 6 mcg/mL | 20 mg/min. for 30 min. | 1.25 mg/min. |

**Children:** (Over one month of age)

**Intramuscular injection:** 10 to 15 mg/kg/day in 2, 3 or 4 equal doses.
*Moderately severe infections:* 15 to 20 mg/kg/day in 3 or 4 equal doses.
*Severe infections:* 20 to 30 mg/kg/day in 3 or 4 equal doses.

**Intravenous Administration:**
*Moderately severe infections:* 15 to 25 mg/kg/day by continuous drip or in 3 or 4 equal doses, each infused over 20 minutes or longer.

*Severe infections:* It is recommended that children be given no less than 300 mg/day regardless of body weight. (Dilute Dalacin C Phosphate Sterile Solution in the same manner as for adults.)

**Dilution and Compatibility:**
4 mL (600 mg) Dalacin C Phosphate when diluted with 1000 mL of the following commonly used infusion solutions was found to be physically compatible and demonstrated no significant change in pH or antimicrobial potency over a period of 24 hours:

Sodium chloride injection
Dextrose 5% in water
Dextrose 5% in saline
Dextrose 5% in Ringer's Solution
Dextrose 5% in half-strength saline plus 40 mEq potassium chloride
Dextrose 2½% in Lactated Ringer's Solution (Hartmann's Solution)

Dalacin C Phosphate was not stable when added to Dextrose 5% in water plus vitamins. Therefore it is not recommended that Dalacin C Phosphate be mixed with any infusion solution containing B vitamins.

**Supplied:**
Dalacin C Phosphate contains the following per mL of sterile solution:
Clindamycin phosphate equivalent to clindamycin base 150 mg
Benzyl alcohol 5 mg
Disodium edetate 0.5 mg
Water for injection q.s.
When necessary the pH is adjusted with sodium hydroxide and/or hydrochloric acid to maintain a pH range of 5.5 to 7.0.
Dalacin C Phosphate is available in 2 mL and 4 mL ampoules.

**NOTE:** Do not store below 15°C.

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# SURGEONS' UPDATE

## Researchers Seek Improved Treatment for Patients Requiring Hip Replacement

A group of researchers at the University of Waterloo, Waterloo, Ont., is searching for ways to improve the results of surface replacement of the hip, a procedure they believe has advantages over the traditional technique of hip replacement.

The group consists of Greg McNeice, a civil engineer with expertise in stress analysis and a bioengineering background, John Medley, a mechanical engineer with a background in biotribology, Wayne Brodland, a specialist in the area of biomechanics, Martine LaBerge, a mechanical engineer whose expertise includes clinical experimentation with biomaterials, particularly in surface replacement for synovial joints, and several students.

Hip replacement, says one of the researchers, has not always provided a permanent solution since "even under the best of circumstances the implant–bone interface may break down after a number of years", but surface replacement has also presented difficulties. Says McNeice, "We've heard of instances where the cap slipped off the end of the bone as early as one year after it was implanted."

The researchers believe that some of the problems with the surface replacement procedure are caused by the material used. The metal cap that is placed over the shaved femoral head does not have the same properties as the bone it replaces, so when the bone is capped "it may become stress-shielded and when this happens, the bone no longer carries normal stress and...it disappears and you get progressive failure". The effect of stresses on the femoral head is one of the problems that will be studied. Softer, more compliant material will be tested for use as the cap or as a layer to be placed between the cap and the bone. The researchers also hope to develop improved methods for cementing the cap to the shaved bone.■

*Contributions to this column are welcome. Please send your material to: Miss Laurel Williamson,* Canadian Journal of Surgery, *PO Box 8650, Ottawa, Ont. K1G 0G8*

## New Director of Training and Evaluation at Royal College

The Royal College of Physicians and Surgeons of Canada has appointed Jean-Pierre DesGroseilliers, FRCPC, as its Director of Training and Evaluation, succeeding Robert F. Maudsley, FRCSC. Dr. DesGrosseilliers comes to the Royal College from the University of Ottawa, where he was Assistant Dean, Faculty of Health Sciences, but has in the past participated on several College committees and survey teams.■

**FIG. 1 — J-P. DesGroseilliers.**

## CJS Coeditor Named 1988 Sims Travelling Professor

Dr. Lloyd D. MacLean, who was appointed the 1988 Sir Arthur Sims Commonwealth Travelling Professor by the Royal College of Surgeons of England, begins his travels this month. During the next 3 months Dr. MacLean will be visiting various centres in New Zealand, Australia, Malaysia and Hong Kong; then in April he will be off again — this time to the British Isles. The Sims Professor's role is both academic — assisting in the advancement of medical science by lecturing, teaching or engaging in research — and ambassadorial.■

## Ontario's Health Ministry Awards Annual Research Grants

The Ontario Ministry of Health recently awarded $5 million to fund 87 new and ongoing health care research projects.

A group at the University of Toronto hopes to improve the outcome of corneal transplant surgery; 20% of corneal transplants fail, the majority during the first year. The researchers will study data on 600

patients, collected by the Corneal Transplant Registry from 18 Ontario surgeons who perform corneal transplants. Factors that can affect success or failure of a transplant, such as the interval between the donor's death and removal of the eye, the interval before surgery and method of storage of the eye between removal and surgery, will be analysed. The study is expected to be completed by early 1991.

A Hamilton research group will study geographic variation in cancer rates across the province of Ontario. They are asking the question — Is there more variation in cancer incidence from one region to another than one would expect by chance? If a substantial variation is found, the researchers will determine if it is possible to link these variations to environmental factors such as water quality, air pollution, terrestrial radiation, urbanization, industrialization or occupation. The study will be based on data collected by the Ontario Cancer Treatment and Research Foundation registry from 1976 to 1985.■

## Multiorgan Transplant Unit Opens in Vancouver

A multiorgan transplant unit, administered jointly by Vancouver General Hospital and the British Columbia Transplant Society, was opened recently by British Columbia Health Minister Peter Dueck. Patients requiring transplant surgery will no longer be required to travel to other provinces or countries. Care will be provided both before and after surgery in the eight-bed unit equipped with state-of-the-art diagnostic and monitoring technology. A budget of $3 680 000 will cover operating costs for the first year and an additional $350 000 will be used to purchase new equipment.■

**Laurel Williamson**

# BOOK REVIEWS

**ANDROLOGY. John P. Pryor and Larry I. Lipshultz. 340 pp. Illust. Butterworth & Co. (Publishers) Ltd., London, 1987. $65.95 (US). ISBN 0-407-02361-5.**

Andrology represents a current review of 12 selected topics related to male reproductive disorders. The subject-oriented format is of value not only to the urologist-in-training but also to the practising general urologist, because this area of urology is taking up increasingly more clinical time.

The topics are well selected to provide a state-of-the-art review of uncommon and specialized subjects, including intersex, hypospadias and epispadias, and the increasingly topical subjects of impotence, infertility and vasectomy. The material is directed primarily to the clinician, giving a more basic discussion of disorders of intersex, ejaculatory disturbances, and hormone function and regulation of the prostate. The chapter on impotence is weak in the area of diagnostic investigation; however, the discussion on the treatment of impotence is extensive and current. All chapters are well referenced and the text is extensively indexed.

This book is an excellent current review of the subject of andrology, it provides outstanding reference material for further study and is presented in a very readable format.

Grant Angus Farrow, MD, FRCSC, FACS

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**BENIGN STRICTURES OF BILE DUCTS. Edward I. Galperin, Nikolai F. Kuzovlev and Suren R. Karagiulian. 345 pp. Illust. International Universities Press, Inc., Madison, Conn., 1987. $60.00 (US). ISBN 0-8236-0494-2.**

This book is written by experienced Russian surgeons who have made biliary tract surgery their specialty. The text is, therefore, a review of the treatment of benign biliary strictures, mostly from their own experience. It includes an overview of the literature on the subject with an emphasis on the Russian literature.

The problem with many translated texts is that the awkwardness of the language makes reading difficult as in this case. The print is clear and there are many excellent diagrams and drawings to supplement the text.

The content flows logically from etiology to clinical manifestations of benign biliary stricture, from there to diagnostic maneuvers, preoperative preparation and finally to principles and practice of surgery for repair. The authors cover many different surgical techniques and express personal preferences. Some areas are controversial, such as long-term stenting of biliary anastomosis; however, in the authors' hands, the results appear to be good. In other parts of the book, such as that on

*continued on page 384*

# Surgeon-Administered Local Anesthesia for Forefoot Surgery

A.A. Giachino, MD, FRCSC

Operating rooms are often not put to full use because of a shortage of anesthetists. However, in certain circumstances the surgeon can safely administer local anesthesia and perform major surgery without complications as demonstrated in this paper.

## Method

Eighty-seven patients underwent 147 procedures which were done on 100 feet.

In all patients history-taking was thorough and physical examination included specific questions regarding allergies to local anesthetic and family history of malignant hyperthermia. All procedures were performed in a regular hospital operating room. In all patients, an intravenous line was established and electrocardiograms and blood pressure monitoring were supervised by the circulating nurse. Xylocaine was the only local anesthetic used and the dosage guidelines set forth in the product monograph (*Xylocaine Parenteral Solutions*; Astra Pharmaceuticals Canada Ltd., Mississauga, Ont.) were followed. The volume of xylocaine without adrenaline did not exceed 4.5 mg/kg and xylocaine with adrenaline, 7 mg/kg.

## Technique

Ankle blocks are performed, beginning on the posteromedial aspect. A 25-gauge needle is positioned posterior to the posterior tibial artery until paresthesia is produced in the region of the heel or forefoot; then 5 ml of local anesthetic is injected (Fig. 1). The saphenous nerve is next anesthetized by palpating it next to the saphenous vein and injecting around it. The deep peroneal nerve is blocked by depositing a small amount of xylocaine just superficial to the ankle joint capsule by way of the interval between extensor hallucis longus and tibialis anterior tendons (Fig. 2). The superficial peroneal nerves are palpated and blocked in a ring block fashion (Fig. 3). The sural nerve is palpated next to the peroneal tubercle and anesthetized by a local injection (Fig. 4), except in patients who are to undergo bunion surgery. For most procedures a tourniquet is applied just proximal to the malleoli and the pressure adjusted to 100 mm Hg above systolic pressure.

## Results

Seventy-one ankle blocks and 21 local infiltrations or digital blocks were performed for a variety of procedures (Table I).

Only one patient, a hysterical teenage girl with a gonococcal infection of the great toe metatarsophalangeal joint needed conversion of the local anesthetic to a general anesthetic. There were no medical complications.

Use of an ankle tourniquet proximal to the area of anesthesia was not a problem. Major forefoot reconstruction such as a combination Fowler and Mayo metatarsal joint excisional arthroplasty and proximal joint fusions was carried out with a tourniquet applied for more than 1 hour and elicited no complaints from the patients.

## Comment

The surgeon can safely and successfully administer local anesthesia for forefoot surgery. A paresthesia must be registered only from the posterior tibial nerve, and once the foot is prepared and draped and an ankle tourniquet applied, access to this nerve is markedly limited. To limit the volume, and thus possible

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toxicity, of the xylocaine, the sural nerve was not anesthetized in bunion surgery, and the patients were told that they would have sensation on the lateral aspect of the foot. When the sural nerve was blocked it was easily palpated and well localized adjacent to the peroneal tubercle. Until the surgeon achieves a high success rate in the administration of the block, a standby anesthetist should be available.■

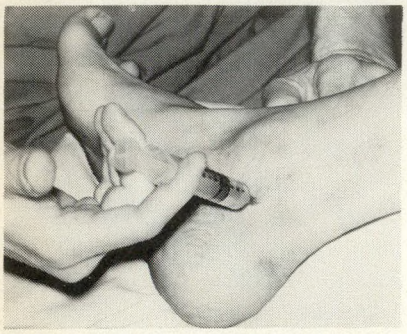

**FIG 1. — Paresthesia produced in heel by injecting 5 ml of xylocaine posterior to posterior tibial artery.**

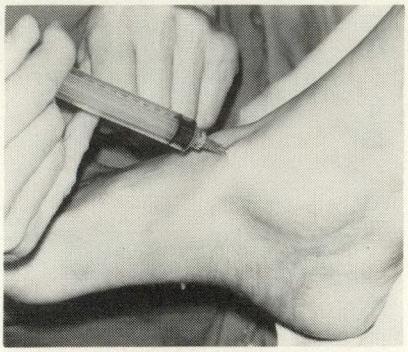

**FIG. 2 — Injection of xylocaine superficial to ankle joint capsule will block deep peroneal nerve.**

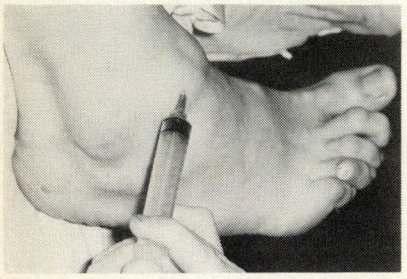

**FIG. 3 — Superficial peroneal nerves are palpated then blocked.**

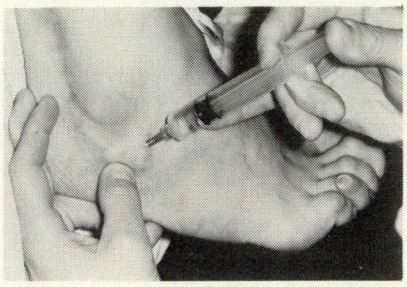

**FIG. 4 — Sural nerve is palpated and blocked.**

**Table I** – Forefoot Procedures Performed

| Procedure | No. |
|---|---|
| Unilateral | |
| Forefoot reconstructions | 16 |
| Bunion procedures | 13 |
| Metatarsal osteotomies | 17 |
| Bunionette excisions | 3 |
| Proximal interphalangeal joint fusions | 12 |
| Exostectomies | 11 |
| Hallux rigidus procedures | 6 |
| Medial sesamoidectomies | 4 |
| Metatarsophalangeal joint synovectomies | 4 |
| Morton's neuroma resections | 2 |
| Ganglion excision | 1 |
| Radical toenail excisions | 11 |
| Miscellaneous | 21 |
| Bilateral | |
| Forefoot reconstructions | 2 |
| Metatarsal osteotomy | 1 |
| Bunion procedures | 2 |
| Combinations | 8 |

## BOOK REVIEWS

*continued from page 382*

preoperative care, there are insights into methods of treatment that would be foreign to most Canadian readers. One example of this is forced diuresis for endotoxemia. One is left wishing to know more about the results of such treatment.

This book will appeal to the subspecialist surgeon or the general surgeon with a particular interest in the bile ducts. There is also a place for it on the shelves of the reference library.

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**GENITOURINARY ULTRASOUND: A TEXT/ATLAS. Edited by Beverly G. Coleman. 542 pp. Illust. Igaku-Shoin Medical Publishers, Inc., New York; W.B. Saunders Company Canada Limited, Toronto, 1988. $95.75. ISBN 0-89640-130-8.**

Ultrasonography has become indispensable in diagnosing and treating benign and malignant genitourinary disease as a result of the great improvement over the past decade in ultrasound techniques and equipment. This atlas documents the various applications of ultrasonography in urinary tract disease. Each ultrasound image is accompanied by a schematic anatomical reproduction and a line drawing to aid in its description and interpretation. The accompanying text is concise and makes for easy viewing and, for the non-ultrasonographer, a remarkably informative teaching tool.

The book covers all aspects of genitourinary disease, including benign and malignant disease in both adults and children and illustrations of interventional techniques. Although the images are well reproduced and extensive, the accompanying text is occasionally mis-

*continued on page 412*

# Symposium on Current Perspectives in the Management of Soft-Tissue Sarcoma

## 1. Incidence, Investigations and Staging of Soft-Tissue Sarcoma

Michael G. Rock, MD, FRCSC

**Soft-tissue sarcomas account for only 1% of all malignant lesions. The Canadian Sarcoma Group encourages the investigation and management of these tumours at tertiary institutions, where a multidisciplinary team can handle the complex problems. Staging of these tumours implies accurate anatomic determination of the extent of disease, the histogenesis and grade of the tumours and the presence of regional or distant metastases. Arteriography, computed tomography and magnetic resonance imaging can accurately define the tumour before biopsy. The biopsy should be muscle-splitting to minimize contamination of additional compartments and should allow inclusion of the biopsy site at definitive surgical resection. It should be done at the institution where definitive management will be performed. Regional lymph-node involvement can be detected using magnetic resonance imaging or gallium scanning, whereas for distant metastases, specifically of lung, computed tomography is the method of choice.**

**To date no one staging system for soft-tissue sarcomas has been universally accepted. A hybrid, encompassing the advantages of each system, is being formulated.**

**Les sarcomes des tissus mous comptent pour seulement 1% de tous les cancers. Le Groupe canadien pour les sarcomes soutient la recherche et le traitement de ces tumeurs dans des institutions de troisième ligne, où des équipes multidisciplinaires peuvent prendre charge de problèmes complexes. L'établissement du stade évolutif de la maladie suppose la détermination anatomique précise de l'étendue de la maladie, l'histogénèse et le stade de la tumeur et la présence de métastases régionales ou éloignées. L'artériographie, la tomodensitométrie et la résonance magnétique nucléaire permettent de définir clairement la tumeur avant la biopsie. La biopsie doit être faite par voie intermusculaire afin de minimiser les risques de contamination de compartiments additionnels et doit permettre d'inclure le point de biopsie lors de la résection chirurgicale définitive. Elle doit être pratiquée dans l'institution où le traitement final sera prodigué. Une atteinte des ganglions régionaux peut être détectée par résonance magnétique nucléaire ou par scintigraphie au gallium, alors que la tomodensitométrie demeure la méthode de choix pour les métastases à distance, particulièrement au poumon.**

**A ce jour, il n'existe pas de système universellement accepté pour déterminer le stade évolutif des sarcomes des tissus mous. Un système hybride, réunissant les avantages de chacun, est en voie d'être formulé.**

Although no accurate statistics exist as to the incidence of soft-tissue sarcomas in Canada, it has been estimated that in the United States there are 5000 new cases annually.

Because of the need for specially trained units to manage the complex problems associated with these tumours, 50 referral centres have been identified in the United States. Unfortunately, this arrangement is not feasible in Canada. To manage 150 to 200 cases a year, quoted as being the volume necessary to maintain expertise in treating these

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*Presented as part of a symposium on current perspectives in the management of soft-tissue sarcomas, by the Royal College in cooperation with the Canadian Oncology Society, the Canadian Orthopaedic Association and the Canadian Association of Radiation Oncology, at the 56th annual meeting of the Royal College of Physicians and Surgeons of Canada, Winnipeg, Man., Sept. 12, 1987*

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tumours,[1] all patients with soft-tissue sarcomas presenting in Canada would have to be referred to three or four major institutions. Realistically, patients with these tumours will continue to be managed in university affiliated tertiary institutions and by capable staff in other hospitals. Thus, all surgeons dealing with these problems must be current in their knowledge of investigation and staging.

At meetings dedicated to the subject, the consensus has been that these tumours should be treated by a multidisciplinary team. Because surgery is the mainstay of management, the surgeon should have the cooperation of radiologists, specialists in nuclear medicine, pathologists, chemotherapists and radiation therapists. Before treatment, the team should identify the anatomic extension of the tumour, the histogenic type and grade, anticipated response of the lesion to other treatments and patient priority regarding such plans.

## Defining the Extent of Disease

Patients with soft-tissue tumours usually present because of the mass effect, which in itself may be asymptomatic, painful, compromise neurovascular structures, decrease mobility of contiguous joints or encroach upon or invade abdominal or pelvic viscera. It is essential to obtain a careful history since exposure to chemical carcinogens such as phenoxyacids, chlorophenols, phenylchloride gas, or long-standing use of anabolic steroids have been known to induce soft-tissue sarcomas, especially hepatomas.[2] Exposure to radiation from outmoded radiotherapy equipment or during administration of variable dosage radiation can, after a long latent period, result in sarcomatous transformation — as with the secondary development of lymphangiosarcomas in long-standing lymphedema after radical breast resection (the Stewart–Trieves syndrome). It is well recognized that patients with von Recklinghausen's disease are predisposed to neurofibrosarcomas.

Laboratory analysis should include a complete blood count, measurement of sedimentation rate, liver enzymes and alkaline phosphatase levels. With large soft-tissue sarcomas in which there is central necrosis and at times local hemorrhage, it is not uncommon for the patient to have a low hemoglobin value, slightly elevated leukocyte count and a significantly elevated blood sedimentation rate. Although the lung is the preferred site of metastases for these tumours, the liver may be involved, compromising heptic function. Alkaline phosphatase determination is necessary when the mass is close to osseous structures, with the potential to invade not only periosteum but also underlying cortex. A bone scan is mandatory in such cases as the area involved must be included in a definitive surgical excision.

Indium and gallium scans give valuable information. The latter is picked up predominantly by the reticuloendothelial system, allowing imaging of the liver and spleen and, more importantly, regional lymph nodes at the tumour site. Unlike its bone counterpart, some soft-tissue sarcomas, notably rhabdomyosarcoma, synovial sarcoma and malignant fibrous histiocytoma will disseminate to regional nodes in 20% to 25% of cases. The indium scan is much more selective for infection, so any mass whose density on other radiologic investigations appears consistent with abscess or hematoma may be more effectively identified.

Dual plain x-ray films are insufficient to identify essential characteristics of the tumour (Fig. 1). Distortion of soft-tissue planes, compartment distortion or even scalloping of underlying bony structures indicating invasion may be noted, but these findings are inadequate when deciding on treatment. Similarly, ultrasonography, although effective in identifying the presence of the mass, will not determine its size, extension or proximity to various muscle groups or neurovascular structures. The most useful information can be obtained from arteriography, computed tomography

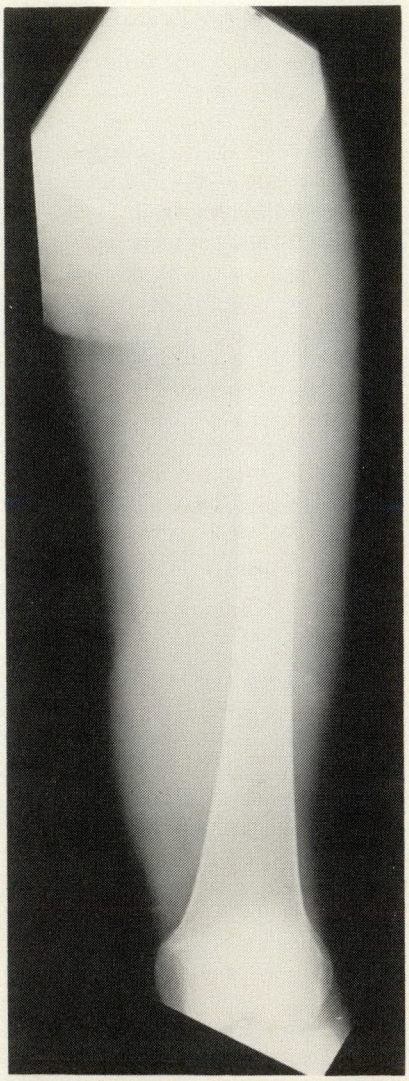

**FIG. 1 — Plain x-ray film of thigh of 35-year-old woman, known to have neurofibromatosis. Ill-defined soft-tissue mass is present medially.**

and magnetic resonance imaging. Arteriography is indicated when soft-tissue tumours adjoin major vascular channels. The early phase of the arteriogram will allow assessment of anatomic or vessel distortion and indicate the vascularity of the lesion; if it appears to be highly vascular it may be prudent to carry out selective embolization of feeding vessels 24 to 48 hours before resection of the mass. The late venous phase allows appreciation of tumour size and its reactive zone, representing the host's attempt to wall off the rapidly growing lesion with a zone of hypervascularity, fibrous tissue and inflammatory cells. This is important information because satellite lesions, having penetrated the pseudocapsule, will sometimes extend into the reactive layer from the principal tumour. This appearance is erroneously conceived by many surgeons as an effective barrier to tumour migration. This surrounding contaminated reactive zone may be left behind in a marginal excision or shelling-out procedure.

With computed tomography it is possible to define the anatomical extension, compromised tissue compartments, consistency of the tumour and its proximity to vital structures (Fig. 2). This is particularly true of intrapelvic and retroperitoneal sarcomas that are extremely difficult to define anatomically by means other than computed tomography or magnetic resonance imaging. Because of the long interval between onset and detection, it is not surprising that 15% of patients have chest metastases at the time of initial presentation.[6] Computed tomography has also revolutionized the assessment of chest metastases among sarcoma patients (Fig. 3), and it now plays one of the principal roles in the staging of these tumours. When taken 5 mm apart, a 3-mm nodule can be imaged with the scanner, giving a sensitivity that is an improvement on the 6-mm pick-up with whole lung tomography. However, the selectivity of the latter is much more accurate. Lesions that are questionably granulomatous necessitate additional tomography to assess the presence of calcification thus favouring granuloma rather than metastasis.

Magnetic resonance imaging represents a marked improvement, even on the information available from computed tomography (Fig. 4). From both axial and coronal cuts, the presence of the tumour and its relationship to surrounding anatomy is much better appreciated. Magnetic resonance imaging is also accurate in identifying fatty tumours that may be malignant and the presence of extra-abdominal desmoid tumours, which have proven difficult to identify with conventional computed tomography because the signals between muscle and tumour are similar. Our current philosophy for extremity, pelvic and retroperitoneal soft-tissue tumours is to favour magnetic resonance imaging while recognizing that computed tomography is more accurate in detecting chest metastases.


FIG. 2 — This 28-year-old man presented with enlarging mass in left buttock. Computed tomography shows large soft-tissue tumour which on open biopsy was identified as high-grade malignant fibrous histiocytoma.

## Defining Histogenic Type and Grade

After appropriate investigations have delineated possible tumour extension, the histogenic type and

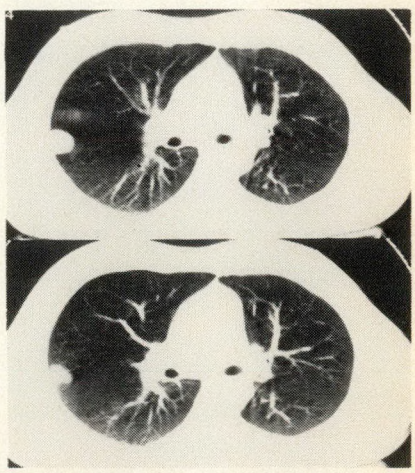

FIG. 3 — Preoperative staging studies of patient from Fig. 2 included computed tomography of chest revealing solitary chest metastasis.

grade of the tumour must be defined. An adequate biopsy must be performed, if possible by the surgeon who will ultimately do the definitive resection. Undoubtedly, there will be situations where excisional biopsies will be performed for what was thought to be a benign lesion, but histologically was proved to be malignant. If there is any suggestion of malignancy, evoked by the size, rapid appearance or symptom complex of the tumour, the patient should be referred, before biopsy, to a centre where the required expertise and ancillary services are available. A recent survey by the Musculoskeletal Tumor Society[3] compared the efficacy of performing a biopsy on a sarcoma in the referring centre and in the treating centre. They found that biopsy related problems occurred three to five times more frequently when performed at a referring institution. The Society members strongly recommended that all aspects of treatment of sarcomas be conducted in a recognized facility capable of managing such patients.[4,5] If this is not feasible, the following guidelines should be observed to minimize the number of confusing biopsy findings:

- In the extremities, flank and pelvic area, place the biopsy skin incision in line with the underlying muscle fibres to avoid compromising subsequent definitive surgical procedures.
- Transverse incisions can make skin coverage difficult after definitive surgical excision. The approach to the underlying tumour should be of muscle-splitting orientation to minimize compartment contamination and hemorrhage, which should be accurately controlled before closure. Representative tissue, which can be determined from preoperative magnetic resonance imaging, should be obtained and confirmed by a pathologist before the biopsy wound is closed.
- Aerobic and anaerobic swabs should be taken at the same time as the biopsy to exclude the possibility of central necrosis with infection in the tumour or the presence of an unrecognized abscess.
- In the recovery room ice packs should be placed around the biopsy area and activity minimized for 24 hours to discourage tracking of hematoma along fascial planes.

The biopsy can be performed by fine needle, needle, excisional or incisional techniques, but the incisional method is preferred. Needle-biopsy material demands that the pathologist makes a diagnosis on cytologic examination alone; this is a very difficult proposition, and definitive histogenic classification is often impossible. It is also more difficult to obtain truly representative sections, to identify the needle tract which must be incorporated in the excision of the tumour, because of contamination. Excisional biopsy leaves residual tumour in the wound with possible contamination of surrounding tissue.

By electron microscopy and immunohistochemical testing a definitive histogenic type and grade of the biopsy specimen can be determined. This is of more than academic interest because the natural history of the various sarcomas is quite different, necessitating altered forms of adjuvant therapy.

## Staging of Disease

Possibly the most contentious and currently debated aspect of soft-tissue sarcomas is the means of staging. The American Joint Committee for Cancer Staging and End Results Reporting has attempted to extrapolate the TNM system, pri-

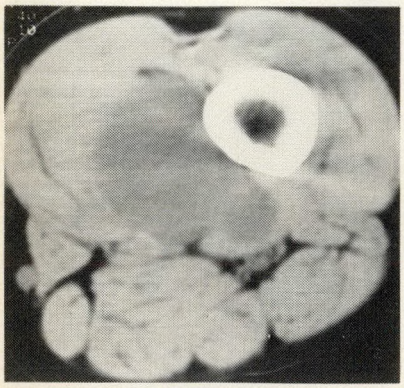

Fig. 4a

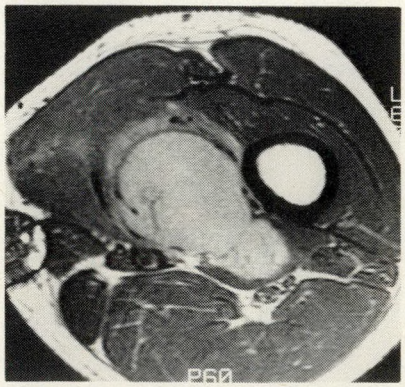

Fig. 4b

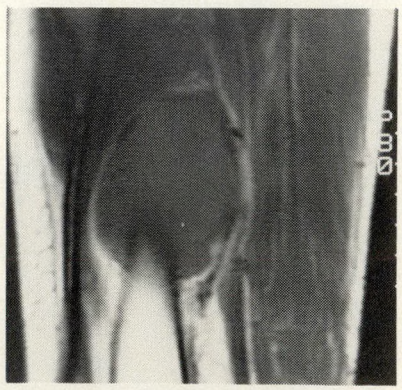

Fig. 4c

**FIG. 4 — (a) Computed tomogram of lesion from patient in Fig. 1 revealed solid tumour deep to adductor muscles extending to underlying femur. (b) Magnetic resonance imaging, coronal cut. Proximity of tumour to superficial femoral vessels and sciatic nerve are better demonstrated. Pseudocapsule and reactive zone around tumour appear more clearly, allowing more accurate preoperative determination of contaminated tissues. (c) Magnetic resonance imaging, sagittal cut. Actual longitudinal extension of tumour. Neurofibrosarcoma was ultimately removed with wide margins.**

marily used for carcinoma, to soft-tissue sarcomas. When the prognostic importance of grade became evident it was included into the staging system which became the GTNM staging system. To physicians managing a large volume of soft-tissue sarcomas it became obvious that the extended TNM classification was not applicable to these tumours. Members of the Musculoskeletal Tumor Society pointed out that there was no link between it and treatment planning. Inconsistencies arose in prognosis, associated with overlap of the various stages, and the nodal metastases introduced at stage III of the disease implied a better prognosis than usually seen with distant lymph-node metastases. Moreover, the majority of physicians managing soft-tissue sarcomas also deal with osseous sarcomas, and the proposed TNM classification for the former is not applicable to the latter. Therefore, the Musculoskeletal Tumor Society proposed an alternative staging system for sarcomas,[1,6] recognizing that surgery was the definitive mode of treatment and thus the staging system should have direct influence on surgical management. Furthermore, it was subsequently proven that there was no intrinsic difference between histogenically similar lesions in soft tissue and bone.

The present staging system used by most orthopedic surgeons dealing with soft-tissue sarcomas is the one subsequently formulated, which maintains simplicity for universal application and clinical correlation with the natural history of these tumours. Briefly, it is a three-stage system based on the grade of the tumour (low G1 or high G2) and whether the tumour is intracompartmental (T1) or extracompartmental (T2). The concept of compartmentalization is important because it has a direct impact on the subsequent surgical management and because most anatomical areas fall within specific compartments. At times (5% of cases), confinement within a given compartment proves difficult and the classification is not as effective. Stage III disease implies distant or nodal metastases, recognizing that both carry a poor prognosis. This three-stage system has been applied to thousands of soft-tissue and bone sarcomas with reproducible prognoses. The orthopedic community and the international Musculoskeletal Tumor Society have universally accepted the Enneking system because of its simplicity and accuracy of prognosis.

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# 2. The Role of Chemotherapy in Multimodality Therapy

Vivien H.C. Bramwell, PhD, MB, BS, FRCPC

**The role of chemotherapy in adult soft-tissue sarcomas is controversial. In this review, the author examines the effectiveness of single-agent and combination chemotherapy to manage advanced disease and the role of adjuvant combination chemotherapy to control primary tumours and prevent the spread of the disease.**

**Doxorubicin (Adriamycin) is still considered the most effective single agent for advanced soft-tissue sarcoma. Ifosfamide has given similar results and may have greater potential in combination therapy than cyclophosphamide. A current study using trimetrexate shows early positive results.**

**Doxorubicin, cyclophosphamide, vincristine and dacarbazine is currently the most efficacious combination.**

**The efficacy of adjuvant chemotherapy remains to be established. The majority of studies indicate some benefit with chemotherapy, particularly in the relapse-free survival rate, but no consistent improvement in overall survival has been noted.**

**Le rôle de la chimiothérapie dans le sarcome des tissus mous de l'adulte est discutable. Cette revue porte sur l'efficacité de la mono et de la polychimiothérapie dans le traitement des cancers à un stade avancé et du rôle de la polychimiothérapie adjuvante dans la maîtrise des tumeurs primitives et dans la prévention de la dissémination de la maladie.**

**La doxorubicine (Adriamycine) est toujours considérée comme le médicament qui, utilisé seul, est le plus actif contre les sarcomes des tissus mous au stade avancé. L'ifosfamide a donné des résultats comparables à ceux de la doxorubicine, et semble présenter de plus grandes possibilités en polychimiothérapie que la cyclophosphamide. Une étude présentement en cours avec le trimetrexate laisse prévoir des résultats positifs.**

**Actuellement, la cyclophosphamide, la vincristine et la dacarbazine représentent l'association la plus active.**

**L'intérêt de la chimiothérapie adjuvante reste à être démontré. La majorité des études indique qu'elle peut être d'un certain apport, particulièrement en ce qui a trait à la survie sans récidive, mais aucune amélioration notable dans la taux de survie n'a été noté.**

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*Presented as part of a symposium on current perspectives in the management of soft-tissue sarcomas, by the Royal College in cooperation with the Canadian Oncology Society, the Canadian Orthopaedic Association and the Canadian Association of Radiation Oncology, at the 56th annual meeting of the Royal College of Physicians and Surgeons of Canada, Winnipeg, Man., Sept. 12, 1987*

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Although chemotherapy is of proven benefit in embryonal rhabdomyosarcomas of childhood, its role in adult soft-tissue sarcomas is more controversial. This review examines the activity of single and combination cytotoxic drugs in advanced disease. The potential contribution of adjuvant chemotherapy in providing local control of primary tumours and preventing metastasis is analysed.

## Advanced Disease

### *Single Agents*

Of the anthracyclines, doxorubicin (Adriamycin [ADR]), introduced into clinical practice in the early 1970s, is generally acknowledged as the most active single agent in the treatment of adult soft-tissue sarcomas. A review of relevant studies containing more than 25 patients,[1-8] showed an average response rate of 24% (range from 16% to 41%) in 930 patients. An intensive search to identify anthracyclines that retain the antitumour efficacy of ADR with less toxicity, especially cardiotoxicity, has been disappointing; Carminomycin,[9] deoxydoxorubicin,[10] Aclacinomycin[11,12] and demethoxydaunorubicin,[13] each showed insignificant activity. When given at identical doses (75 mg/m$^2$ every 3 weeks) in a study performed by the European Organisation for Re-

search and Treatment of Cancer (EORTC), Epiadriamycin was less toxic than ADR, but the response rate was lower — 15 of 84 (18%) versus 21 of 83 (25%) for ADR.[14] This difference was not statistically significant, but it is unlikely that Epiadriamycin, even if used at a dose equitoxic to ADR, will be more active.

With respect to alkylating agents, ifosfamide, an interesting analogue of cyclophosphamide, was synthesized in Germany in 1967. Reported response rates are available on 218 patients treated with a variety of doses and schedules of ifosfamide.[15] The average rate of 28% (range from 18% to 38%) is remarkably similar to that for ADR.[16] However ifosfamide has been evaluated in considerably fewer patients, and characteristically the response rate of a new drug is inversely proportional to the number of patients in which it is evaluated. Nevertheless, ifosfamide, in contrast to ADR, has been used more frequently as second-line chemotherapy. Response rates in an EORTC study comparing ifosfamide with cyclophosphamide were 18% and 8% respectively[17] and provided the only single-agent data for cyclophosphamide. Ifosfamide produced two responses in 28 previously treated patients and three responses in 31 patients crossed over after failure of cyclophosphamide. The response rates for patients who had never received chemotherapy were 10 of 40 (25%) for ifosfamide and 5 of 38 (13%) for cyclophosphamide. Although the rates were not significantly different by conventional statistical analysis, ifosfamide caused less myelosuppression than cyclophosphamide, suggesting greater potential in combination.

Of other single agents, it is generally accepted that dacarbazine (DTIC) shows limited activity in soft-tissue sarcomas,[18,19] the average response rate in accumulated series (97 patients) being 18% (range from 15% to 25%). Cisplatinum is very active in osteosarcoma and has been extensively tested in soft-tissue sarcoma.[2,3,5] An average response rate of 9% in 150 patients does not warrant inclusion in combination chemotherapy, particularly as it is a very toxic and expensive drug. The data on methotrexate are intriguing. A study from the United Kingdom[20] reported a response rate of 25% in 62 patients. A variety of doses, routes and schedules were used in this trial. A later EORTC study was unable to demonstrate any activity for methotrexate given intravenously every week in previously treated patients.[21] Although high-dose methotrexate has been used in several small series,[1] there is no evidence that its activity is increased, and no group has repeated the studies of conventional-dose methotrexate. The Canadian Sarcoma Group, in conjunction with the National Cancer Institute of Canada, is currently performing a phase II study using trimetrexate, a methotrexate analogue, and responses have been seen.

**Table I** – Response to Combination Chemotherapy

| Combination | No. of patients | Response, % |
|---|---|---|
| CYVADIC* | 750 | 48 (15–68) |
| ADR/DTIC | 592 | 27.5 (20–42) |
| CYCLO/VCR/ADR | 70 | 19 |
| CYCLO/ADR/DTIC | 80 | 35 |
| CYCLO/VCR/ADR/DACT | 199 | 40 |
| CYCLO/ADR/MTX | 100 | 36 |

*Cyclophosphamide, vincristine, Adriamycin, dacarbazine.
ADR = Adriamycin, DTIC = dacarbazine, CYCLO = cyclophosphamide, VCR = vincristine, DACT = actinomycin D, MTX = methotrexate.

**Table II** – Combination Chemotherapy Including Ifosfamide

| Series | Combination | No. of patients | Response, % |
|---|---|---|---|
| Wiltshaw and associates, 1986[23] | ADR + IFOS | 47 | 36 |
| Schutte and associates, 1986[22] | ADR + IFOS | 178 | 36 |
| Elias and Antman, 1986[24] | ADR + IFOS + DTIC | 65 | 52 |

ADR = Adriamycin, IFOS = ifosfamide, DTIC = dacarbazine.

### *Combination Chemotherapy*

The drug combination most commonly used to treat adult soft-tissue sarcomas is CYVADIC (Table I). It consists of cyclophosphamide (500 mg/m$^2$), vincristine (1.4 mg/m$^2$, day 1), ADR (50 mg/m$^2$) and dacarbazine (250 mg/m$^2$, days 1 to 5).[1–8] The two most active single agents (ADR and dacarbazine) have also been used fairly extensively in combination,[2,6] but the response rate (Table I) seems lower than that of CYVADIC. Other ADR combinations have activity in the same range, but none are better than CYVADIC.[1–8]

The addition of ifosfamide to ADR[22,23] has been disappointing (Table II). In the EORTC study[22] of 178 patients treated with ADR and ifosfamide, the overall response rate of 36% was similar to that reported for CYVADIC (39%). However, nearly half the patients receiving CYVADIC manifested disease progression, whereas the corresponding figure for ADR and ifosfamide was 19%. The addition of dacarbazine seemed to improve the response rate.[24] However, this particular regimen was very myelosup-

pressive; there was a 23% incidence of granulocytopenic fever. A central venous line had to be inserted in all patients and treatment was given by intravenous infusion for 5 days every 3 weeks.

The EORTC is currently comparing ADR, CYVADIC and ADR plus ifosfamide in a three-arm study; 393 patients have been entered in 22 months and the accrual should be complete within 6 months. Comparative response rates are not yet available, but should be very interesting as ADR has never been directly compared with CYVADIC. This study should also clarify the value of ifosfamide used in combination.

The Canadian Sarcoma Group is performing a pilot study of the combination of ADR, ifosfamide and dacarbazine, using a shorter, more convenient schedule than the Boston group. The Boston group is comparing their schedule of this combination with ADR alone.

## Primary Management

### *Intra-arterial Chemotherapy*

To improve local control, chemotherapy has been given intra-arterially in conjunction with surgery and radiotherapy. There have been no randomized studies comparing this route of therapy with other methods for local control, such as radical surgery or limited surgery plus radiotherapy. Investigators claiming superiority for intra-arterial therapy have generally compared their results with historical controls from their own centre or results reported in the literature, both of which have obvious flaws.

Another method of primary management has been that of isolation perfusion with or without hyperthermia. Most studies using this method were performed between 1960 and 1980 with drugs such as melphalan, actinomycin D and nitrogen mustard, whose activity in soft-tissue sarcomas is minimal. The results of several of these series[25-28] are compared in Table III with the results reported by Lindberg and colleagues[29] from a group of patients treated by surgery and radiotherapy in a major centre. Limb salvage, local recurrence and ultimate outcome in terms of overall survival, show little advantage for the complex, expensive and cumbersome technique of isolation perfusion.

The intra-arterial use of ADR with or without radiotherapy preoperatively has been reported (Table IV).[30-32] Eilber's group[33,34] has the most extensive experience and their rates of limb salvage and local control are impressive. However, complications, including pathologic fracture of long bones, led them to reduce the dose of radiotherapy in

**Table III** – Isolation Perfusion With Melphalan, Actinomycin D and Nitrogen Mustard Plus Hyperthermia Compared With Surgery Plus Radiotherapy

| Series | No. of patients | Limb salvage, % | Local recurrence, % | Metastases, % | Overall survival, % |
|---|---|---|---|---|---|
| Chemotherapy | | | | | |
| Stehlin and associates, 1984[25] | 65 | 94 | NS | NS | 73 |
| Lehti and associates, 1986[26] | 64 | 83 | 11 | 33 | 67 |
| McBride, 1976[27] | 85 | 89 | 15 | 23 | 68 |
| Krementz and associates, 1977[28] | 73 | 90 | 25 | 30 | 64 |
| No chemotherapy | | | | | |
| Lindberg and associates, 1981[29] | 200 | 85 | 20 | 25 | 69 |

NS = not stated.

**Table IV** – Intra-arterial Adriamycin With Radiotherapy Compared With Preoperative and Postoperative Radiotherapy Without Chemotherapy

| Series | No. of patients | Follow-up, mo. | Limb salvage, % | Local recurrence, % | Metastases, % | Overall survival, % |
|---|---|---|---|---|---|---|
| Chemotherapy | | | | | | |
| Mantravadi and associates, 1984[30] | 32 | 15 | 91 | 3 | 25 | 70 |
| Denton and associates, 1984[31] | 15 | 24 | 80 | 6 | NS | 79 |
| Goodnight and associates, 1985[32] | 17 | 32 | 88 | 0 | 35 | 82 |
| Eilber and associates, 1984[33] 1985[34] | | | | | | |
| Protocol 2 | 77 | 60 | 96 | 4 | NS | 64 |
| Protocol 3 | 105 | 24 | 97 | 8 | NS | 95 |
| No chemotherapy | | | | | | |
| Karakousis and associates, 1986[35] | 85 | >24 | 96 | 13 | NS | 68 |
| Abbatucci and associates. 1986[36] | 89 | 60 | 93 | 14 | NS | 66 |

NS = not stated.

protocol 3 (from 3500 rad in 10 fractions to 1750 rad) and this doubled the local recurrence rate. Judging from the results of protocol 2, the rate of metastasis was not affected by improved local control and the survival rate may not be better. Protocol 3 still has a very short follow-up. When the results of preoperative and postoperative irradiation as in the studies by Karakousis and associates[35] and Abbutucci and colleagues,[36] are used for comparison (Table IV), the local recurrence rates with radiotherapy only are slightly higher, but the outcome is otherwise similar, again casting doubt on the value of intra-arterial chemotherapy. Eilber's group is currently conducting a randomized trial comparing intra-arterial versus intravenous preoperative chemotherapy, and it may be that the theoretical advantages of intra-arterial chemotherapy will not be clinically evident.

*Systemic Adjuvant Chemotherapy*

Since the frequency of soft-tissue sarcoma is approximately 2 in 100 000, the difficulties of performing good randomized studies of adjuvant chemotherapy in this heterogeneous group of tumours are obvious. Most studies published or in progress are flawed.

To examine the role of adjuvant ADR, the results of five randomized studies[37-41] are summarized (Table V); each of them compares a chemotherapy group with a randomized control group treated only by surgery with or without radiotherapy. The Scandinavian study of Alvegard[40] is the largest but has been reported only in abstract form and the follow-up is relatively short. Nevertheless, it has the greatest power to detect differences between the two arms, and the various prognostic factors are more likely to be evenly distributed. The Boston/ECOG study of Wilson and colleagues[41] has much longer follow-up than the other studies, and although there was a slight delay in the appearance of metastases in the ADR arm, there have been no significant differences in disease-free survival or overall survival for all patients or those with extremity sarcomas only.

**Table V** – Randomized Studies of Adjuvant Adriamycin

| Series | No. of patients | Median follow-up, mo | Outcome |
|---|---|---|---|
| Gherlinzoni and associates, 1986[37] | 59 | 28 | RFS $p < 0.005$ in favour of ADR. No data on overall survival |
| Antman and associates, 1987[38] | 64 | 20 | NS |
| Eilber and associates, 1986[39] | 114 | 30 | NS |
| Alvegard, 1986[40] | 146 | 36 | NS |
| Wilson and associates, 1986[41] | 75 | 49 | NS |

RFS = relapse-free survival, NS = not significant.

**Table VI** – Randomized Studies of Adjuvant Combination Chemotherapy

| Series | Combination | No. of patients | Median follow-up, mo | Outcome |
|---|---|---|---|---|
| Edmonson and associates (Mayo Clinic), 1984[44] | VCR/DACT/CYCLO alternating VCR/ADR/DTIC 12 mo | 61 | 64 | NS |
| Lindberg and associates (M.D. Anderson Hospital), 1976[45] | VCR/ADR/CYCLO | 43 | 120 | RFS, $p = 0.04$ in favour of chemotherapy OS NS |
| Benjamin and associates (M.D. Anderson Hospital), 1987[46] | VCR/DACT/CYCLO 24 mo | | | |
| Rosenberg and associates (National Cancer Institute), 1985[47] | ADR/CYCLO/HDMTX 14 mo | 65 | 60 | RFS and OS, $p = 0.04$ in favour of chemotherapy |
| Bramwell and associates, 1987[48] | CYVADIC 8 mo | 317 | 37 | RFS, $p = 0.01$ in favour of chemotherapy OS NS |

NS = not significant, OS = overall survival, HDMTX = high-dose methotrexate.

The only study giving positive results, that of Gherlinzoni and colleagues from Bologna,[37] has been severely criticized.[42] The number of patients was relatively small and there were three different surgical groups. These factors, combined with a poor randomization technique, led to considerable imbalance in prognostic factors between the arms. A recent update of this study,[43] involving 77 patients (33 receiving ADR and 44 controls), demonstrated improvement in relapse-free and overall survival for the ADR treated group, but the median duration of follow-up was not stated.

At present there is no firm evidence that adjuvant single-agent ADR affords any substantial benefit in soft-tissue sarcomas. However, delay in the appearance of metastases in some studies suggests that more aggressive chemotherapy may be worth pursuing.

Randomized studies of various types of combination chemotherapy versus control are depicted in Table VI.[44-48]

The first study was performed by Lindberg and colleagues at the

M.D. Anderson Hospital and Tumor Institute in the early 1970s and reported after 18 months' follow-up.[45] At that time, the chemotherapy group was doing slightly, although not significantly, worse. Recently this study has been reanalysed after 10 years' follow-up.[46] The relapse-free survival now favours the chemotherapy group, but although overall survival is better for that group, the difference is not significant. Local recurrence was lower in the chemotherapy arm (two versus eight), but metastases occurred with similar frequency — 45% (9 of 20) in the chemotherapy group versus 48% (11 of 23) in controls.

Because the early results of the M.D. Anderson Hospital study were negative, the trial from the United States National Cancer Institute was the first randomized study[47] to suggest benefit for adjuvant chemotherapy. It should be emphasized that this study had serious flaws — the number of patients was very small, increasing the likelihood of imbalance of known and, more importantly, unknown prognostic factors between the arms; the control group has done worse than expected when compared with results reported by other centres, thus magnifying the difference between the two arms. Because the ADR dose was pushed to tolerance there was a 30% incidence of subclinical cardiomyopathy detected by nuclear medicine scans, and three patients suffered congestive heart failure. Benefit was observed only in extremity sarcomas; the same chemotherapy had no effect in head, neck and trunk sarcomas. The most recent analysis,[49] with median follow-up of 7 years, no longer demonstrates improved survival for the chemotherapy group ($p = 0.124$).

Building on the results of their previous study,[47] and dismayed by the high incidence of cardiomyopathy, Rosenberg and colleagues compared their "standard" chemotherapy with an abbreviated course of treatment, giving much lower total doses of ADR and cyclophosphamide and omitting high-dose methotrexate.[49] There were no significant differences between the two treatments, in terms of 5-year disease-free (72%) and overall (75%) survival. In view of the lack of efficacy of ADR as an adjuvant, and the minimal activity of cyclophosphamide in advanced disease, it would be surprising if this combination proves to be effective.

A Mayo Clinic study[44] did not demonstrate any benefit for adjuvant chemotherapy, but the incidence of local recurrence (30%) was high in this trial, perhaps because radiotherapy was not used. In addition, the chemotherapy used was inadequate — the vincristine, actinomycin D, cyclosphosphamide combination is inactive in advanced disease, and as vincristine, ADR, dacarbazine was only alternated every 6 weeks with the first combination, patients received active drugs only every 12 weeks, and at a low dose intensity.

For all patients in the EORTC study,[48] there was a significant improvement in relapse-free survival in the CYVADIC arm ($p = 0.01$), although this is of borderline significance on subgroup analysis by site, for both limb sarcomas ($p = 0.06$) and those of the head, neck and trunk ($p = 0.09$). However, there was no benefit for any group in terms of overall survival. In fact, the improvement in relapse-free survival was entirely accounted for by reduced local recurrence in the CYVADIC arm ($p = 0.005$) whereas distant metastases occurred with equal frequency in both arms ($p = 0.28$). It is intriguing that the reduction in local recurrence seems to be occurring in head, neck and trunk tumours.

## Conclusions

Although the majority of studies suggest some limited benefit for adjuvant chemotherapy, the optimal regimen and timing of such therapy remain to be established. The conclusions of the National Institutes of Health Consensus Development Conference on Bone and Soft-Tissue Sarcomas, 1984, remain relevant — "the efficacy of adjuvant systemic chemotherapy for high grade sarcomas remains to be established within the context of prospective clinical trials."[50]

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# SESAP V Question

**Items 253–255**

A 54-year-old man has noted an increase in the size of his left thigh over the last 18 months. Physical examination reveals a fairly well-circumscribed, rubbery, nontender, 9.0- × 5.0-cm mass on the medial aspect of the thigh, noticeably more prominent with the knee extended. The patient has no history of trauma or recent infection.

**253.** The procedure LEAST likely to aid in management of this patient is

(A) conventional roentgenography of the thigh

(B) angiography

(C) ultrasonography of the thigh

(D) computed tomography of the thigh

(E) lymphangiography

**254.** A soft tissue mass is demonstrated in a subfascial plane of the thigh. The most appropriate method for determining the histopathology would be

(A) multiple percutaneous aspiration needle biopsies

(B) incisional biopsy

(C) "core" needle biopsy

(D) enucleation of the lesion for biopsy

(E) wide local excision

**255.** Pathologic examination shows liposarcoma. Definitive treatment might include each of the following EXCEPT

(A) wide anatomic soft-part resection

(B) adjuvant postoperative radiotherapy

(C) adjuvant postoperative chemotherapy

(D) preoperative radiation therapy

(E) preoperative systemic chemotherapy

For the incomplete statements above, select the one completion for each that is best of the five given.

For the critique of Items 253–255 see page 426.

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# 3. Limb-Sparing Management in Extremity Soft-Tissue Sarcomas in the Adult: the Radiation Oncologist's Viewpoint

Brian O'Sullivan, MB, FRCPC

**Current management of extremity soft-tissue sarcomas achieves local control in a high proportion of patients. This paper describes the local methods to conserve limb function that have largely replaced traditional approaches of ablative surgery. Frequently, these methods employ conservative surgery with preoperative or postoperative radiotherapy. An understanding of the biology and behaviour of these rare tumours is necessary to optimize the goals of limb conservation without compromising local control. Appropriate surgical and radiotherapy techniques are facilitated by planned pretreatment staging methods and communication between the surgical and radiation oncology teams. Although a high rate of local control can be expected, distant metastases continue to be a problem. Future strategies should be directed towards scheduling of optimal local treatments with the investigation of adjuvant systemic methods to reduce the rate of distant metastases.**

**Le traitement actuel des sarcomes des tissus mous des membres assure une cure locale chez un grand nombre de malades. Cet article décrit les moyens utilisés localement pour conserver la fonction du membre, lesquels ont largement remplacé l'approche traditionnelle de chirurgie ablative. Souvent, ces méthodes ont recours à une chirurgie conservatrice accompagnée d'une radiothérapie pré- et postopératoire. Il est nécessaire de bien connaître la biologie et le comportement de ces tumeurs rares, si l'on veut optimiser l'objectif de conserver le membre sans compromettre la cure locale. Les techniques chirurgicales et radiothérapeutiques appropriées sont rendues plus faciles par une planification des méthodes employées avant traitement pour évaluer le stade évolutif de la maladie, et par une bonne communication entre les équipes de chirurgie et de radiothérapie. Même si on peut s'attendre à un bon taux de cures locales, les métastases à distance demeurent un problème. Dans l'avenir, les stratégies devront viser à établir un programme des traitements locaux optimums, tout en cherchant les thérapies adjuvantes systémiques destinées à réduire le taux des métastases à distance.**

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Thirty years ago Cade[1,2] noted that radiotherapy combined with surgery was of greater value than surgery alone in treating soft-tissue sarcoma of the extremities. Because of a long-standing misconception that these tumours were resistant to radiotherapy,[3] the mainstay of management continued to be radical surgical excision, often consisting of limb amputation, and only recently have Cade's observations been widely accepted. An understanding of certain biologic, technical and behavioural features of these lesions and their treatment has resulted in a modified philosophy toward management. This discussion focuses on some of these issues, provides evidence for the efficacy of adjuvant radiotherapy in a conservative surgical approach and describes the radiotherapy options and methods of administration.

## Biologic Issues of Importance for Radiotherapy

### *The Compartmental Nature of Soft-Tissue Sarcomas*

Soft-tissue sarcomas typically respect fascial boundaries, intermuscular septae, bones, tendons and joint capsules. As a result, tumour enlargement in most cases remains confined to the compartment of

origin and occurs centifugally along fascial planes. Extracompartmental spread by direct invasion is uncommon but may be seen in very large or neglected lesions. Usually it results from an extracompartmental origin de novo or from diagnostic (biopsy) or therapeutic (resection) interventions, which have breached a fascial boundary. Lesions arising de novo in intercompartmental spaces (extracompartmentally) pose specific problems for both surgeon and radiation oncologist in their choice of appropriate resection or radiation volumes. Such sites include the femoral triangle, popliteal fossa and antecubital fossa, axilla and subcutaneous tissues where distinct barriers to tumour spread are not present. Management of compartmental lesions, on the other hand, can make use of the localized nature of the tumour, thereby sparing unnecessary resection. Local treatment must be planned with knowledge of the precise localization of the tumour and the areas at risk for subclinical disease. Where available, magnetic resonance imaging and computed tomography help to identify the anatomic extent of the disease and also any important structures that may be involved in the dissection. Together with the operative and pathology reports, initial imaging information is also useful when planning subsequent postoperative radiotherapy fields.

*Regional Node Involvement*

Regional lymph nodes are involved in only 3% to 5% of adults with an extremity lesion,[4] an exception being epithelioid sarcoma, for which rates approaching 50% have been quoted for synchronous and metachronous nodal disease.[5] However, regional node dissections and deliberate inclusion of nodes within radiation treatment portals are not routine. To do this would compound the technical problems involved in providing optimal preservation of limb function because of complications relating to surgery and radiotherapy.

*The Capsule or Pseudocapsule*

Unfortunately there is no defined anatomic capsule to provide a local barrier to tumour spread. On the contrary, the apparent "capsule" is nothing more than a layer of compressed normal tissue created by the rapid centrifugal expansion of tumour. This layer is invaded by microaggregates of tumour as is the surrounding reactive zone of peripheral normal tissue (Figs. 1 and 2). Similar microaggregates can be expected to exist some distance from the margins of gross tumour and may form tumour satellites or micrometastases in higher grade lesions. Furthermore, if the pseudocapsule has been penetrated during surgery, areas around the dissection site or involved in residual hematoma will likely harbour tumour cells.[6] This explains local failure after both conservative and radical procedures involving marginal tumour removal. For the same reasons, if gross tumour is visible within the wound it can be accepted that tumour seeding has occurred, even if the affected area is subsequently totally resected through the same incision. These concepts also explain "field edge" local failures after postoperative radiotherapy, when tumour cells may have migrated some distance along fascial planes during the dissection, in postsurgical hematoma or primarily as micrometastases.[6]

*Specific Pathologic Details*

There is agreement that similar management approaches are required for the individual histologic subtypes of soft-tissue sarcoma. Although different histologic subtypes may occur more commonly in

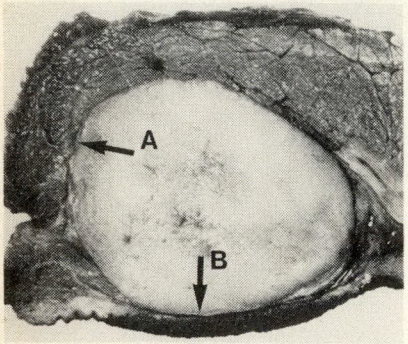


**FIG. 1 — Gross specimen of fibrosarcoma after compartmental resection. Tumour is growing into surrounding muscle (A) on most of surface where it has formed pseudocapsule. Fascial layer contains growth (B) in remaining area.**

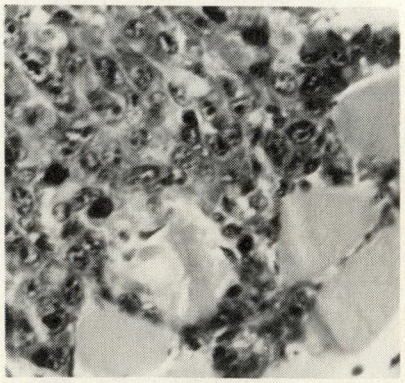

Fig. 2a

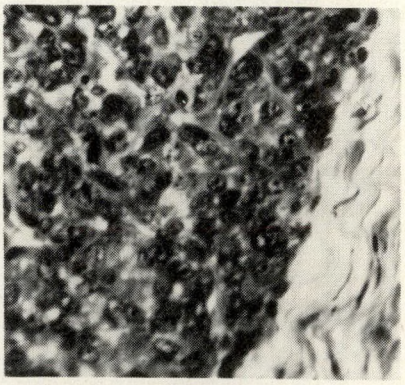

Fig. 2b

**FIG. 2 — (a) Part of pseudocapsule shows tumour cells infiltrating and interdigitating between muscle fibres. (b) Fascial area shows tumour contained by true barrier to tumour spread (hematoxylin and eosin, original magnification × 200).**

certain age groups or anatomic sites, their behaviour is more closely linked to tumour size and grade. Indeed, alterations in management have been suggested, depending on the grade of the lesion; higher doses and larger volumes are favoured for higher grade lesions.[7] Microscopic findings of incomplete removal are indications for further treatment; further surgical removal should be attempted when feasible and is usually combined with adjuvant preoperative or postoperative radiotherapy. In surgical resections that included radical margins of healthy tissue (minimum 2 cm), the benefit of radiotherapy is unproven.

## Adjuvant Radiotherapy

### *Goals of Treatment*

Table I[4,8] describes the expected outcome of surgery as the only treatment. The terms used conform to accepted terminology[8] for procedures ranging from intralesional, marginal and wide excisions to more radical forms of surgery with variable amounts of tumour residuum. Both local and ablative surgical excisions may be described by these terms. An ablative operation including a radical margin of healthy tissue is expected to provide at least 80% local control of the primary lesion; if such margins cannot be obtained this level of control cannot be achieved and the tumour may be better managed by using combined approaches. Satisfactory outcomes for conservative limb-sparing surgery alone or in combination with adjuvant radiotherapy should preserve limb function at an acceptable level of risk and also retain local control and survival rates similar to those of ablative surgery.

### *Principles in Adjuvant Radiotherapy*

Gross tumour can be controlled by radiotherapy alone, but the results are inferior to those achieved by conventional approaches.[9] Surgery alone necessitates radical margins (2 cm minimum); if lesser margins are planned, adjuvant radiotherapy should be considered. In any treatment decision, it should be realized that a satisfactory functional result may be achieved by conservative resection with preoperative radiotherapy instead of postoperative radiotherapy for an ablative procedure with inadequate margins. In the latter case, the patient has received combined modality treatment without the benefits of limb conservation.[10]

Strategies for the combined use of radiotherapy and surgical resection include preoperative,[10,11] postoperative,[12–14] intraoperative[10] and brachytherapy techniques.[15] Preoperative radiotherapy has been combined with intra-arterial chemotherapy,[16,17] and frequently postoperative "boosts" are included. Altered fractionation regimens have also been described for both preoperative (with[16] and without chemotherapy[18]) and postoperative schedules.[19] The method of administration of radiotherapy is governed by a combination of factors, including referral pattern, institutional policies and the available resources.

Table II demonstrates pooled data for the use of adjuvant radiotherapy compared with radical surgery. The important feature demonstrated is the excellent local control achieved regardless of the adjuvant treatment used. Survival outcome is not prejudiced by conservative combined modality approaches compared with radical surgery.[20]

Table III illustrates the relative merits of preoperative and postoperative radiotherapy. In general, a smaller volume of normal tissue requires treatment if the therapy is administered preoperatively; postoperative treatment must include a margin of normal tissue beyond the limit of surgical dissection. Thus,

**Table I** – Local Control After Surgery as the Sole Modality*

| Procedure† | Definition | Consequences | Local failure, % |
|---|---|---|---|
| Intralesional | Incision through pseudocapsule | Residual gross tumour. All tissues contaminated | 90 – 100 |
| Excisional (marginal) | Pseudocapsule removed | "Shell-out": microscopic tumour remains | 80 – 90 |
| Wide | Removal with "normal" tissue | Frequently leaves microscopic tumour | 50 |
| Radical | Removal with uninvolved anatomic barrier (≥ 2 cm) | No residual tumour | 0 – 20 |

*Data from Simon and Enneking[8] and Leibel.[4]
†Terminology describes features of surgical margin not technique of removal.

**Table II** – Patterns of Failure for Radical Surgery Alone and Conservative Surgery with Postoperative Radiotherapy

| | No. of cases | Local failure and distant metastases, % | Distant metastases, % |
|---|---|---|---|
| Radical surgery and/or amputation alone | 464 | 18.1 | 31.5 |
| Conservative surgery and postop radiotherapy | 416 | 18.3 | 22.6 |

*Data from Suit and colleagues.[10]

all skin incisions and tissue planes that have been disrupted during the procedure are at risk from contamination by tumour satellites and skip lesions and require inclusion within the zone of irradiation. This may necessitate treatment to otherwise uninvolved regions including joints, an entire limb circumference or extensive length of an extremity. Furthermore, a planned preoperative course assists communication between treating surgeons and radiation oncologists; surgical procedures are discussed beforehand with knowledge of the proposed tissues to be irradiated, and the topography of surgical scars can be planned with precision. Radiation treatment portals can be reviewed in conjunction with the diagnostic x-ray films and histologic findings. In this manner difficult management issues can be minimized.

Postoperative referral for radiotherapy may be associated with procedures that counteract the goals of limb-sparing treatment. If preoperative imaging has not documented the tumour location and if the patient has not been assessed beforehand by the radiation oncologist, irradiation volumes tend to be excessive. Unplanned surgical approaches may result in transverse incisions crossing from involved to uninvolved compartments, and drain sites positioned in unsatisfactory locations; these may significantly expand the potential regions of contamination and the width of limb requiring treatment. Consequent irradiation can result in painful fibrosis, distal edema and loss of function, which may ultimately lead to limb amputation. Another consideration is the availability of a final pathology report when using postoperative radiotherapy. This is a theoretical advantage because the management approach should be determined beforehand based on the initial incisional biopsy. Rarely, wound healing may be delayed by preoperative therapy and after extensive or complicated surgery in the absence of radiotherapy. In the latter situation, one is faced with the dilemma of an unhealed wound that may contain active tumour, and the need to delay therapy to allow the wound to mature. Since active tumour seedings will be present at the tumour margins, preoperative treatment allows combined therapy to be completed in the shortest time and problems of wound healing can be considered knowing the threat of tumour regrowth is less.

Finally, preoperative and postoperative radiotherapy, although providing essentially similar rates of local control, are not truly comparable. Suit and associates[10] showed that their patients who received preoperative therapy had a greater number of lesions larger than 10 cm in dimension (43% versus 18% for postoperative therapy). Although prospective comparison may present a useful clinical exercise, its feasibility would be affected by the number of "inoperable" cases that could not be managed in a postoperative regimen, requiring preoperative treatment as the only realistic approach and thereby rendering interpretation of the results difficult.

*Technical Factors and Radiotherapy*

For the radiation oncologist, soft-tissue sarcomas present challenging but time-consuming treatment plans. Management of other forms of malignant disease usually utilizes standard treatment, involving radiation fields determined by variations around conventional anatomic landmarks. In contradistinction, extremity soft-tissue sarcomas are atypical, and therapy is outlined according to the principle of sparing a maximum volume of normal tissue while encompassing an acceptable target volume.

Optimal dose delivery usually involves the use of several beams and different qualities of radiation (i.e., photons, electrons or interstitial implants). Beam configurations should be assessed initially on a simulator (a diagnostic-like x-ray unit designed to mimic the precise geometry of the chosen therapy machine). Fluoroscopy and roentgenography to demonstrate beam arrangements are additional features of this process. Verification port films on the treatment machine are then taken before treatment begins. In general, the goal of the therapy is the administration of a moderate dose (e.g., 50 Gy in 25 treatments) to a volume judged to contain microscopic amounts of tumour. This volume will differ, depending on whether the situation is preoperative or postoperative. Most authors recommend margins ranging from 5 to 10 cm beyond involved tissues and advise the larger volumes for high-grade lesions.[7,21] Higher doses are administered by reduced portals to tissues at higher risk (the surgical bed and scars) to provide mini-

**Table III** – Issues in Preoperative and Postoperative Radiotherapy Scheduling

| Issue | Preoperative | Postoperative |
|---|---|---|
| Interspecialty communication | Excellent | Frequently absent |
| Tumour control probability | Excellent | Very good |
| "Inoperable" disease | Standard | Preop required |
| Wound healing | Potential delay | Affected solely by surgical extent |
| Radiotherapy volume | Minimum | Determined by surgical extent |
| Pathology details | Biopsy only | Full specimen |
| Functional outcome | Small radiation volume may enhance | Acceptable |

mum tumour doses of 60 Gy in 30 treatments for low-grade lesions and 66 Gy in 33 treatments for the higher grade lesions.[7]

The initial volume should include all surgical scars and the tumour area determined clinically and by computed tomography and magnetic resonance imaging. Postoperative treatment is facilitated by surgical clips inserted at the tumour site (Fig. 3). Radiotherapy planning is assisted by computerized dosimetry interphasing with computed tomographic images of the patient in the treatment position. This allows the optimal choice of radiotherapy volume (Fig. 4). As far as possible, a generous longitudinal strip of the limb circumference is protected during treatment to avoid circumferential fibrosis and distal edema. Immobilization of the limb may enhance repetition of the daily treatment plan. Beam modification by compensators and wedge filters may contribute to a more uniform distribution of dose within the chosen region by correcting for irregularities in patient contour. Other beam modifiers include shields, which exclude tissues from the treatment volume, and a tissue-like bolus medium, which allows the dose to be placed on the surface of scars and grafted regions when using skin-sparing megavoltage (greater than 1 MeV) photon and electron beam treatment.

*Brachytherapy*

Excellent local control has been reported at Memorial Sloan Kettering Center[15] by combining conservative limb-sparing surgery with postoperative tumour bed irradiation using iridium-192. The procedure involves the postoperative insertion of iridium sources into the tumour bed 72 hours after loading catheters are positioned, 1 cm apart, at the time of surgery. Doses of approximately 40 Gy are administered over 4 to 5 days and have shown local control rates approaching 100%.[15] The method offers an alternative effective means of sparing the limb, but because it involves a commitment to brachytherapy techniques including technical expertise and necessary cooperation between a large group of different specialties, it is not practised in many centres.

*Indications for Radiotherapy*

Although "close" or positive margins of surgical resection represent indications for radiotherapy, there is no uniform agreement that radiotherapy should be carried out in all such cases. Further surgical resection may be indicated before radiotherapy is administered if the margins of resection are indeed inadequate.

In their study, the Roswell Park Group[12] omitted radiotherapy in pa-

Fig. 3a

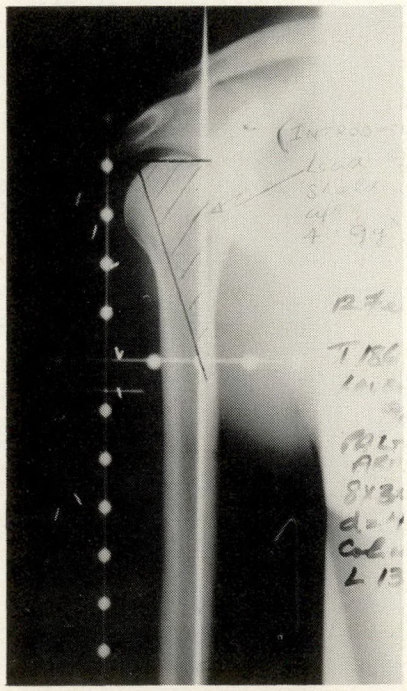

Fig. 3b

**FIG. 3 — (a) Patient in prone position receiving postoperative radiotherapy for tumour originating in left deltoid region. Megavoltage photons are directed to spare medial side of left upper arm. (Field is defined by light field of treatment unit.) Note longitudinal scar positioned in lateral deltoid area. (b) Simulator film. Clips define surgical bed. Shield is to be introduced after dose of 40 Gy to protect humoral head and shoulder joint.**

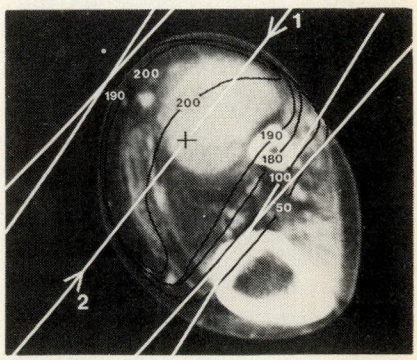


**FIG. 4 — Preoperative radiotherapy treatment plan for malignant fibrous histiocytoma in lateral compartment of lower leg. Surgeon believed lesion could not be resected without entering all three compartments of leg. Preoperative treatment permits anterior compartment to be spared. This would have been impossible postoperatively. (Field arrangement: two opposed cobalt-60 beams 10 × 15 cm.)**

tients whose tumours were resected with a minimum margin of 2 cm. The 5-year local control rates for this group (83%) compared favourably (93%) with a group who received postoperative radiotherapy after tumour resection in which the margins were less than 2 cm. Details of prognostic factors (grade and size for both groups and microscopic residuum for the group with margins less than 2 cm) were not provided for the two groups separately. These data suggest that a 2-cm margin may be safe for resection alone, although, in the absence of information to the contrary, caution should still be exercised for large and high-grade lesions.

At the other extreme of patients having tumour resection with "close" margins, is the patient with microscopic involvement of resection margins. Leibel and associates[13] suggested that postoperative radiotherapy can effectively sterilize "microscopic or small amounts of visible tumour at the margin". Despite this report, postoperative radiotherapy, after incomplete surgery, has had an adverse effect on local control in several reports, including a retrospective series (Bell RS, O'Sullivan B: Unpublished data, 1988) from The Princess Margaret Hospital in Toronto (Fig. 5). Four groups were identified according to whether the margins of resection were microscopically involved, and whether the margins were achieved by a single or multiple surgical procedures (excluding biopsy). For the combined group with microscopic involvement of resection margins, the 5-year actuarial local control rate was 50% and the outcome for the two subsets was not significantly altered by the number of surgical procedures. For the group with clear margins, regardless of how close these were, the figure was 92% and remained uninfluenced by a second procedure performed to obtain negative margins. The detrimental effect of involved surgical margins on local control was independent of other known adverse factors, including tumour grade and size.

Two series[10,20] reported unfavourable local control rates when disease was present in the margins of resection. Incomplete surgery and postoperative radiotherapy for lesions staged IIB, IIIB, and IVA provided 5-year actuarial local control of 58%, compared with 75% for similar-stage recurrent disease and 83% for complete resection.[10] Rosenberg and colleagues[20] reported greater likelihood of local recurrence if resection margins were positive than if they were negative ($p < 0.0001$), despite the use of radiotherapy postoperatively.

## Normal Tissue Effects After Limb-Sparing Treatment

Criteria for assessing limb function have varied between series and the literature contains no confident statements based on prospective data. Nevertheless, acceptable function can be expected in 80% to 90% of patients after radiotherapy and surgical resection, although this rate will vary depending on the nature of the underlying disease process, the extent of surgical resection and the volume of radiation administered. Series in which preoperative radiotherapy was used[10,16,17] had higher complication rates (more than 10%) than those in which postoperative radiotherapy was used (6.5%).[14] This may be because of delayed wound healing after the former but is more likely owing to larger tumours requiring more extensive surgery.

## Conclusions

Extremity sarcomas represent a rare group of malignant lesions. The combined efforts of many different medical disciplines have succeeded in improving management over the past 20 years, mainly in the area of local control where similar rates of control and survival have been achieved by limb-sparing methods and by ablative surgery. Unfortunately metastases still devel-

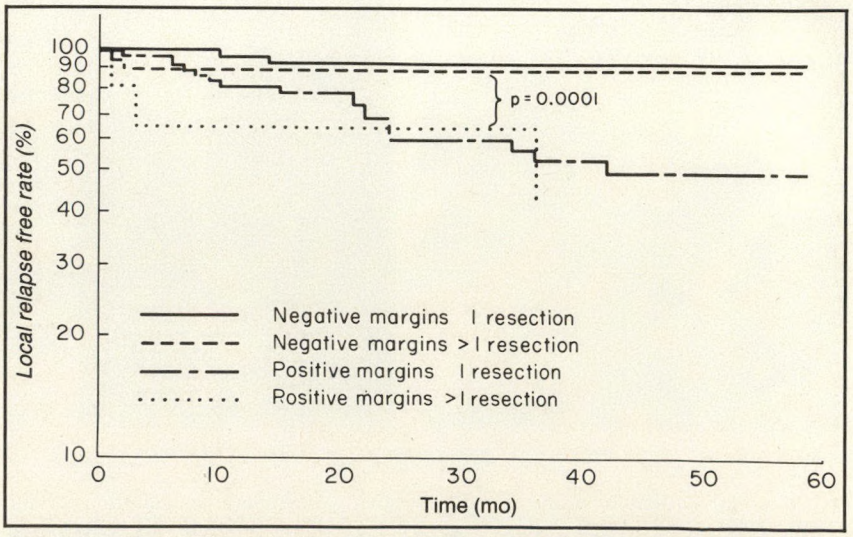


**FIG. 5 — Effect of resection margins on local control. Relapse-free rate for patients with gross tumour resection who received adjuvant radiotherapy. Patients were divided into four groups depending on involvement of surgical margins and whether one or more procedures were used.**

op rapidly in high-risk patients. Future efforts should be directed toward more effective systemic adjuvant therapy — innovations are needed in scheduling radiotherapy and chemotherapy to integrate these two modalities with surgery. In this manner, patient survival may be enhanced without danger of compromising local control and functional outcome.

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## BOOKS RECEIVED

This list is an acknowledgement of books received. It does not preclude review at a later date.

**The Basic Science of Vascular Surgery.** Edited by Joseph M. Giordano, Hugh H. Trout, III and Ralph G. DePalma. 773 pp. Illust. Futura Publishing Co., Inc., Mount Kisco, New York, 1988. $89.00 (US). ISBN 0-87993-321-6.

**Breast Cancer. Collaborative Management.** Edited by Jay K. Harness, Harold A. Oberman, Allen S. Lichter, Dorit D. Adler and Robert L. Cody. 390 pp. Illust. Lewis Publishers, Inc., Chelsea, Mich., 1988. $69.95 (US). ISBN 0-87371-106-8.

**Essential Surgical Practice.** 2nd edition. Edited by A. Cuschieri, G.R. Giles and A.R. Moosa. 1438 pp. Illust. Butterworth International Edition, Stoneham, Mass., 1988. $125.00 (US). ISBN 0-7236-1127-0.

**Metabolic Complications of Acute Arterial Occlusions and Related Conditions (Myonephropathic-Metabolic Syndrome).** Henry Haimovici. 328 pp. Illust. Futura Publishing Co., Inc., Mount Kisco, New York, 1988. $45.00 (US). ISBN 0-87993-324-0.

**Obstetric Anesthesia: the Complicated Patient.** Edited by Francis M. James, III, A. Scott Wheeler and David M. Dewan. 577 pp. Illust. F.A. Davis Company, Philadelphia, 1988. $79.00 (US). ISBN 0-8036-4914-2.

**Operative Ultrasonography During Hepatobiliary and Pancreatic Surgery.** Edited by B. Deixonne and F-M. Lopez. 134 pp. Illust. Springer-Verlag, Berlin; Springer-Verlag New York, Inc., Secaucus, NJ, 1988. $89.50 (US). ISBN 0-387-17630-6.

**Perspectives in Radiology.** Edited by Clyde A. Helms. 166 pp. Illust. Quality Medical Publishing, Inc., St. Louis, Mo., 1988. $171.00. ISSN 0896-873-X.

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# 4. Role of the Pathologist in the Management of Soft-Tissue Sarcomas

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**The contribution of the pathologist to the management of soft-tissue sarcomas is threefold. First, and most important, is to establish the correct pathological diagnosis which should include the histologic type, subtype and grade of the tumour. This information, correlated with the size, site, clinical and radiologic presentation, is the key factor in determining the biologic behaviour of the tumour. As soft-tissue sarcomas frequently demonstrate histologic variability from one area to another, biopsy with computed tomography or radiologic guidance and adequate sampling is essential.**

**Second, careful marking of the surgical resection margins in consultation with the surgeon is necessary to determine the completeness of excision.**

**Third, examination of the resected specimen may also provide useful information on the sensitivity of the sarcoma to any previous radiation or chemotherapy which the patient may have received.**

**La contribution du pathologiste au traitement des sarcomes des tissus mous se fait sentir à trois niveaux. En premier lieu, contribution la plus importante, il y a l'établissement d'un diagnostic précis, comprenant le type et le sous-type histologiques, ainsi que le stade évolutif de la tumeur. Cette information, mise en corrélation avec la taille, la localisation et le tableau clinique et radiologique, est primordiale pour déterminer le comportement biologique de la tumeur. Comme les sarcomes des tissus mous manifestent souvent une variabilité histologique d'une région à l'autre, il est essentiel de pratiquer sous contrôle tomodensitométrique ou radiologique, une biopsie avec prélèvement adéquat.**

**Second apport, la délimination soigneuse de la marge de résection chirurgicale, établie en collaboration avec le chirurgien, est nécessaire pour permettre une excision complète.**

**Troisièmement, l'examen du matériel réséqué peut aussi fournir une information utile sur la sensibilité du sarcome aux traitements radiologiques ou chimiothérapeutiques qu'aurait pu recevoir le malade, préalablement.**

*From the Cancer Control Agency of British Columbia, Vancouver, BC*

*Presented as part of a symposium on current perspectives in the management of soft-tissue sarcomas, by the Royal College in cooperation with the Canadian Oncology Society, the Canadian Orthopaedic Association and the Canadian Association of Radiation Oncology, at the 56th annual meeting of the Royal College of Physicians and Surgeons of Canada, Winnipeg, Man., Sept. 12, 1987*

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The pathologist's contribution to the management of patients with soft-tissue sarcomas is in making the correct diagnosis and expressing the characteristics of the tumour in such a way that the management team has a clear understanding of its biologic potential. An appreciation of the local regional growth patterns and the potential of metastatic spread are essential in planning the type and sequence of the various treatments.

## Behaviour

To evaluate the behaviour of a soft-tissue sarcoma, one needs to know the cell type, grade, mitotic rate, size, depth and site. These factors, considered together, are the most useful prognostic indicators. In general, the smaller and the more superficial the tumour is, the less likelihood there is that metastases will develop. Similarly, tumours located distally tend to metastasize less frequently than more proximal lesions that frequently are deeply placed, large and of high grade.[1-4] It is not surprising that tumours situated deep within the soft tissues tend to be larger at the time of diagnosis as they are less likely to be noticed by the patient and frequently are misinterpreted initially as being reactive processes. Failure to consider a soft-tissue sarcoma in the initial differential diagnosis is

surprisingly common.[5] This may result in an inappropriately placed biopsy incision or an incomplete local incision, both of which may compromise the subsequent definitive surgery and increase the amount of potentially contaminated normal tissue that must be removed to ensure adequate margins.

Soft-tissue sarcomas are rarely truly encapsulated but may be surrounded by pseudocapsule of compressed normal tissues and a reactive zone, giving a clinical impression of encapsulation. They usually display infiltrating margins with tongues of tumour which may, on occasion, extend several centimetres beyond the palpable disease. Malignant fibrous histiocytoma and dermatofibrosarcoma protuberans are examples of such tumours; both tend to grow along fascial planes in a diffuse permeative fashion that the surgeon may not notice.[1,2] This accounts for the multiple recurrences frequently seen adjacent to or within scars of previous incomplete excisions. A superficially placed malignant fibrous histiocytoma that has not penetrated the fascia seldom metastasizes.[1,2] Multiple recurrences may lead eventually to dedifferentiation or recurrence of the higher grade components of the tumour which precede metastatic spread.[6,7] Attempted enucleation or piecemeal excision of soft-tissue sarcomas usually fails, but when a carefully planned excision is undertaken with preoperative evaluation of the tumour by computed tomography or magnetic resonance imaging and a knowledge of the pathologic features and pattern of spread, local control is achieved in the majority of patients without amputation.

## Typing

Many sarcomas may be subtyped according to their histologic pattern. The subtypes frequently correlate with the nuclear grade of the tumour. For example, within the liposarcoma category, a low-grade well-differentiated lipoma-like subtype, a moderate-grade myxoid liposarcoma or high-grade pleomorphic or lipoblastic subtype may be recognized.[1,2] The first two subtypes infrequently metastasize, whereas the pleomorphic or round-cell lipoblastic type of liposarcoma frequently does.[1,2] Sarcomas are often heterogeneous, a single lesion presenting with a variety of subtypes and variable histologic grade.[1,2] It is important to realize this, as a single-needle core or aspirate may not be representative of the entire lesion. Focal necrosis may also be present.

The usual metastatic pattern of spread of a sarcoma is to lung and bone, with infrequent involvement of regional nodes.[1,2] For example, the histologic pattern reflects the pattern of metastatic spread as well as the metastatic potential. In contrast to the usual metastatic spread, synovial sarcomas may metastasize to the regional lymph nodes in approximately 20% of cases and have a tendency to spread along tenosynovial and aponeurotic planes in a discontinuous fashion.[1,2] The surgeon must understand their behaviour and carefully examine the regional lymph nodes and the tenosynovial plane resection margins to ensure completeness of excision. A preoperative computed tomogram may be helpful, as may frozen sections from the resection margins at the time of definitive surgery. Embryonal and alveolar rhabdomyosarcomas also frequently metastasize to regional nodes,[1,2] whereas the adult pleomorphic type infrequently does.[1,2] Some soft-tissue sarcomas may have an unusual metastatic pattern, such as epithelioid sarcomas which may metastasize to the soft tissue of the scalp.[1,2] Although locally aggressive, many soft-tissue sarcomas are late to invade the deep fascial planes and tend to displace the neurovascular bundles;[1,2] both these features may be delineated on the computed tomogram. High-grade small cell tumours, such as lymphomas and neuroepithelioid lesions, are more permeative, surrounding and less frequently displacing neurovascular bundles, than the large cell pleomorphic sarcomas such as liposarcomas and fibrous histiocytomas.[1,2]

## Diagnosis

The differential diagnosis of soft-tissue sarcomas depends on the site of the lesion and the age of the patient;[1,2] it is much more likely that the soft-tissue sarcoma in a child will be a small-celled high-grade one such as an embryonal sarcoma, neuroblastoma, lymphoma or Ewing's sarcoma than in an adult in whom such lesions, apart from lymphomas, are infrequent.[1,2] For a precise diagnosis and correct evaluation of biologic potential, it is important that the tumour be adequately sampled. This can best be achieved by consultation between the radiologist, surgeon and pathologist, who together can evaluate the radiologic appearance of the tumour and plan the areas to be sampled, choosing areas of different texture, both close to the "capsule" and deep within the tumour, so that the biopsy material obtained is representative of the entire lesion.

## Tumour Sampling

Various techniques may be used to obtain a sample of tumour. Fine-needle aspiration may be helpful initially in determining whether the lesion is a soft-tissue tumour rather than an abscess or a reactive proc-

ess. Great caution is required, however, in interpreting such aspirates, because highly mitotic, highly cellular reactive proliferative lesions such as necrotizing fasciitis, pseudosarcomatous fasciitis and myositis ossificans may be easily misinterpreted as a high-grade malignant lesion. Needle biopsies that yield generous cores of tissue or open biopsies are preferred for diagnosis because they allow better histologic evaluation of the tumour. In addition to the routine processing of tumours, electron microscopy, immunologic staining, including monoclonal stains, flow cytometry and chromosomal analysis may all be helpful in arriving at a definitive diagnosis. In order to utilize these techniques, a variety of fixatives may be desirable. The surgeon should alert the pathologist of the time of biopsy and the pathologist should either obtain the specimen directly from the operating room in an unfixed state or have the specimen sent immediately in transport medium to the laboratory for processing. If this is not possible, the pathologist should be consulted as to the desired fixative or fixatives to be used in each case.

## Evaluation of Resection Margins

Similarly, there should be close cooperation between the surgeon and pathologist in the evaluation of the resection margins of the excised specimen. In order to do this thoroughly, it will help if the surgeon orients the specimen for the pathologist, indicating the resection margins of greatest concern. It should be remembered that when fascial planes are incised by the surgeon, the fascial tissues tend to retract, exposing adjacent muscular or fatty tissues which did not constitute the true excision margin. If the pathologist cannot evaluate this and does not have the surgeon's assistance to do so, he may inappropriately mark margins that are thought to represent excision margins. A variety of solutions may be used to mark the excision margins; these include India ink, silver nitrate and laundry bluing, the latter being nontoxic and easy to handle.

## Radiotherapy and Chemotherapy

Additional information as to the extent of residual disease and lymphatic, vascular or neural invasion may help to determine the need for further therapy. If radiotherapy or chemotherapy have already been administered, a comparison of the degree of tumour necrosis, residual viable disease and persistent mitotic activity relative to the original specimen may provide an estimate of the degree of effectiveness of the therapy that the patient received. Various grading systems to evaluate cell damage have been proposed and have been reported to be useful in evaluating osteogenic sarcomas. The effect of the treatment on the adjacent normal tissues can also be evaluated, although morphologic evidence of the vascular damage, which is so important in determining long-term radiation reactions, often is not perceptible until 3 months or more after the initiation of radiotherapy.

## Summary

The pathologist has an important role to play in both the diagnosis and management of patients with soft-tissue sarcoma. Optimally, there should be consultation between the radiologist, pathologist, surgeon and oncologist starting before the initial biopsy investigation so that the biopsy and subsequent surgical management can be well planned and chemotherapy and radiotherapy appropriately integrated into the overall treatment regimen.

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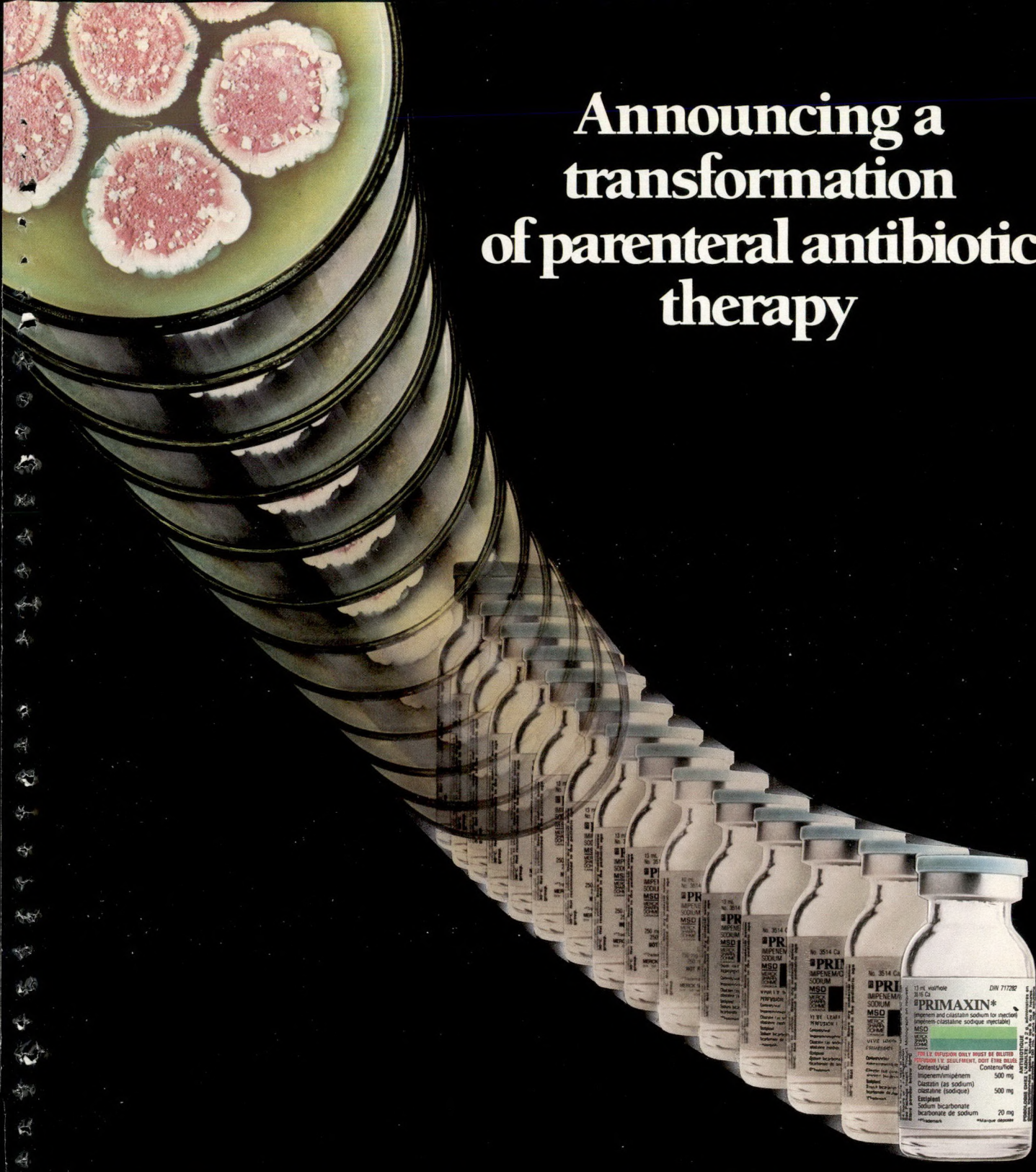



# Announcing a transformation of parenteral antibiotic therapy

# PRIMAXIN* I.V.

(imipenem and cilastatin sodium for injection)

## the first carbapenem antibiotic

* ® Trademark

# PRIMAXIN* I.V.

(imipenem and cilastatin sodium for injection)

A carbapenem, representing a totally new class of antibiotics

## The broadest spectrum single-agent antibiotic

possessing bactericidal activity against a great majority of clinically significant pathogens

PRIMAXIN* offers the activity of

the penicillins against gram-positive aerobes – including coverage of *Streptococcus faecalis*

***plus***

the aminoglycosides and 3rd generation cephalosporins against gram-negative aerobes – including coverage of *Pseudomonas aeruginosa*

***plus***

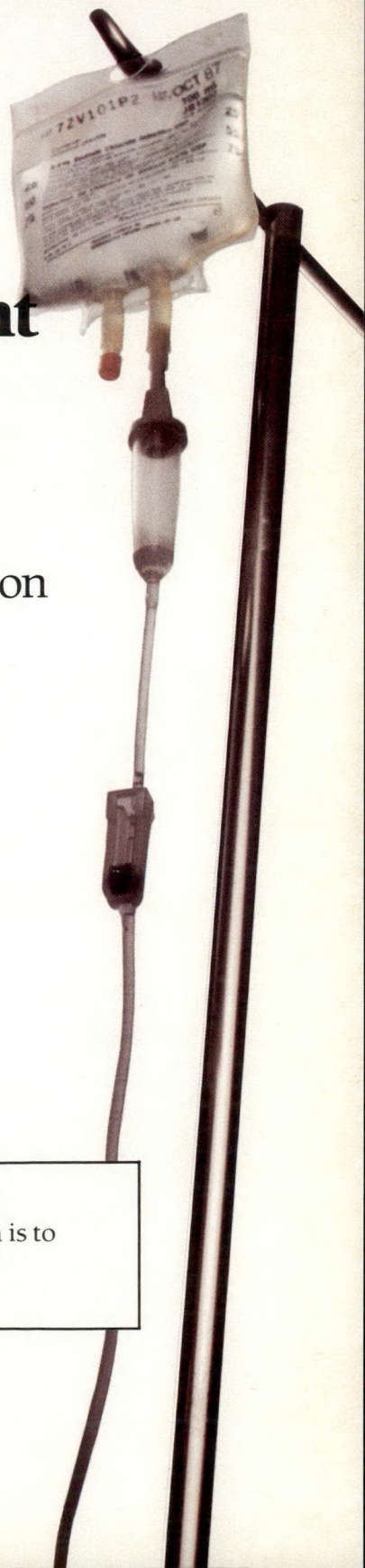
the antianaerobic agents – including coverage of *Bacteroides fragilis*

PRIMAXIN* is not active against *Corynebacterium* group JK, *Fusobacterium varium, Mycobacterium* spp., *Chlamydia* spp., *Streptococcus faecium, Pseudomonas maltophilia,* and some strains of: *P. cepacia, P. pseudomallei,* methicillin-resistant staphylococci, and *Flavobacterium* spp.

# Single-agent antibiotic for documented and empiric therapy in many important infections†

## *including*

- infections usually treated with combination therapy
- infections complicated by underlying disease
- nosocomial infections

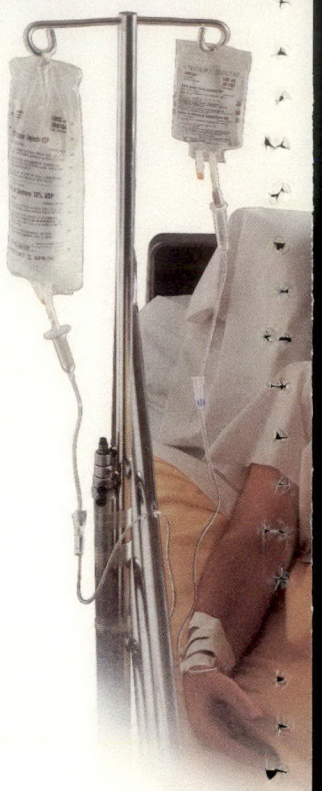


Imipenem and cilastatin sodium are present in a 1:1 ratio in PRIMAXIN* I.V. Imipenem is the sole antibacterial component. The role of cilastatin sodium is to prevent the inactivation of imipenem in the kidney and obtain antibacterial concentrations of imipenem in the urine.

†Caused by organisms susceptible to PRIMAXIN* I.V.

# PRIMAXIN* I.V.

(imipenem and cilastatin sodium for injection)



# Clinical efficacy in many important infections†

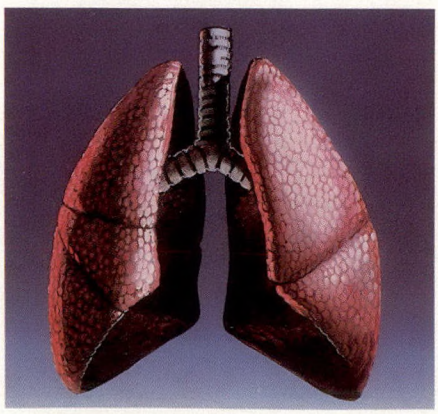
## EFFICACY IN INTRA-ABDOMINAL INFECTIONS[1]

**91% cure or improvement**

in 164 evaluable patients


1. Kager, L., Nord, C.E.: Imipenem/cilastatin in the treatment of intra-abdominal infections: A review of worldwide experience, Rev Infect Dis 7 *(Suppl 3)*: S518-S521, July-August 1985.


## EFFICACY IN LOWER RESPIRATORY TRACT INFECTIONS[2]



**85% cure or improvement**

in 204 evaluable patients

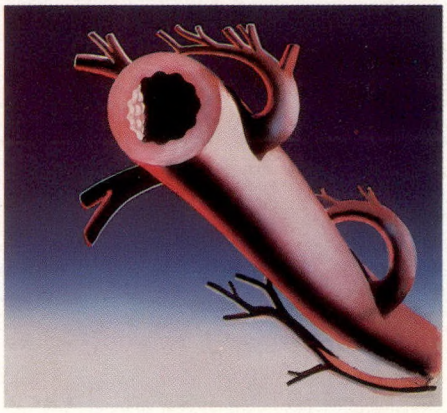

2. Acar, J.F.: Therapy for lower respiratory tract infections with imipenem/cilastatin: A review of worldwide experience, Rev Infect Dis 7 *(Suppl 3)*: S513-S517, July-August 1985.


†Caused by organisms susceptible to PRIMAXIN* I.V.

## EFFICACY IN BACTERIAL SEPTICEMIA[3]

**90% cure or improvement**
in 135 evaluable patients

3. Eron, L.J.: Imipenem/cilastatin therapy of bacteremia, Am J Med *78 (Suppl 6A)*: 95-99, June 7, 1985.



## EFFICACY IN GYNECOLOGICAL INFECTIONS[4]

**97% cure or improvement**
in 72 evaluable patients

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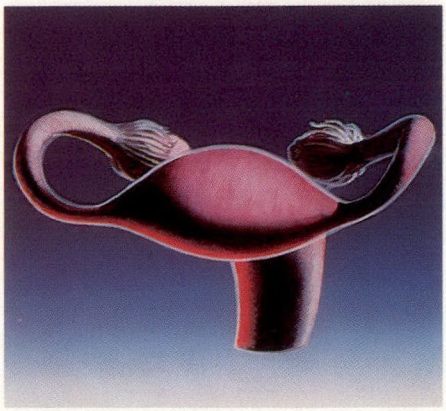

# PRIMAXIN* I.V.

(imipenem and cilastatin sodium for injection)

## PRIMAXIN* I.V. offers management advantages over combination therapy that includes an aminoglycoside

## Generally well tolerated – safety profile similar to cefazolin[5]

- 1723 patients, including the severely ill, have received therapy in clinical trials. The incidence of the most common adverse experience (nausea) was no greater than 2%.
- Avoids the potential nephrotoxicity or ototoxicity experienced with aminoglycosides.
- Avoids the potential hypoprothrombinemia and clinical bleeding experienced with cephalosporins with MTT† side chain.
- Avoids the potential disulfiram-like effect experienced with metronidazole and cephalosporins with MTT side chain.

## Convenience of a single agent

## The broadest spectrum single-agent antibiotic representing a transformation of parenteral antibiotic therapy

5. Calandra G.B., Ricci F.M., Wang C., Brown K.R.: Safety and tolerance comparison of imipenem/cilastatin to cephalothin and cefazolin, J Antimicrob Chemother *12 (suppl D)*: 125-131, 1983.

† Certain antibiotics which possess, as part of their molecular structure, the 1-methyl-5-thiotetrazole (MTT) group have been associated with hypoprothrombinemia (and in some cases, clinical bleeding) and with a disulfiram-like effect.

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# PRIMAXIN*

**(imipenem and cilastatin sodium for injection)**

**Antibiotic**

CNS adverse experiences such as myoclonic activity, confusional states, or seizures have been reported with PRIMAXIN* especially when recommended dosages based on renal function and body weight were exceeded. These experiences have occurred most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) and/or who have compromised renal function. However, there were rare reports in which there was no recognized or documented underlying CNS disorder. Close adherence to recommended dosage schedules is urged, especially in patients with known factors that predispose to seizures.

## ACTION

Imipenem exerts a bactericidal action by inhibiting cell wall synthesis in aerobic and anaerobic gram-positive and gram-negative bacteria.

PRIMAXIN* consists of two components: (1) imipenem, a derivative of thienamycin, a carbapenem antibiotic; and (2) cilastatin sodium, a specific inhibitor of dehydropeptidase-I a renal enzyme which metabolizes and inactivates imipenem. Cilastatin blocks the metabolism of imipenem in the kidney, so that concomitant administration of imipenem and cilastatin allows antibacterial levels of imipenem to be attained in the urine.

Inhibition of cell-wall synthesis is achieved in gram-negative bacteria by the binding of imipenem to penicillin binding proteins (PBPs). In the case of *Escherichia coli* and selected strains of *Pseudomonas aeruginosa*, imipenem has been shown to have highest affinity for PBP-2, PBP-1a and PBP-1b, with lower activity against PBP-3. The preferential binding of imipenem on PBP-2 and PBP-1b leads to direct conversion of the individual cell to a spheroplast resulting in rapid lysis and cell death without filament formation. When imipenem is removed prior to complete killing of gram-negative species, the remaining viable cells show a measurable lag, termed a "post-antibiotic effect" (PAE), prior to resumption of new growth.

## INDICATIONS AND CLINICAL USE

PRIMAXIN* (imipenem and cilastatin sodium for injection) may be indicated in the treatment of serious infections when caused by sensitive strains of bacteria. Where considered necessary, therapy may be initiated on the basis of clinical judgment before results of sensitivity testings are available. Continuation of therapy should be reevaluated on the basis of bacteriological findings and of the patient's clinical condition.

Imipenem is active *in vitro* against a wide range of gram-positive and gram-negative aerobic and anaerobic bacteria, including most strains which are beta-lactamase producing. Patients have responded while under treatment with PRIMAXIN* for single or mixed infections of the following body systems, when they were associated with a number of pathogenic species and strains of the genera listed:

1. Lower Respiratory Tract Infections
2. Urinary Tract Infections
3. Intra-Abdominal Infections
4. Gynecological Infections
5. Septicemia
6. Endocarditis caused by *Staphylococcus aureus*
7. Bone and Joint Infections
8. Skin Structure Infections

**Gram-positive Aerobes**

- *Listeria monocytogenes*
- *Nocardia asteroides*
- *Staphylococcus* (excluding many strains which are methicillin resistant)
- *Streptococcus* (excluding *S. faecium*)

**Gram-negative Aerobes**

- *Acinetobacter*
- *Citrobacter*
- *Enterobacter*
- *Escherichia coli*
- *Haemophilus influenzae*
- *Haemophilus parainfluenzae*
- *Klebsiella*
- *Morganella morganii*
- *Neisseria*
- *Proteus* (indole positive and indole negative strains)
- *Providencia*
- *Pseudomonas aeruginosa*
- *Serratia marcescens*

**Gram-positive Anaerobes**

- *Clostridium* (excluding *C. difficile*)
- *Peptococcus*
- *Peptostreptococcus*

**Gram-negative Anaerobes**

- *Bacteroides fragilis*
- *Bacteroides* (non-fragilis)

## CONTRAINDICATIONS

PRIMAXIN* (imipenem and cilastatin sodium for injection) is contraindicated in patients who have shown hypersensitivity to either component of this product.

## WARNINGS

PRIMAXIN* (imipenem and cilastatin sodium for injection) SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO STRUCTURALLY-RELATED DRUGS. IF AN ALLERGIC REACTION TO PRIMAXIN* OCCURS, DISCONTINUE THE DRUG. SERIOUS HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

**Pseudomembranous colitis**

Pseudomembranous colitis has been reported with the use of PRIMAXIN*. Therefore it is important to consider this diagnosis in patients who develop diarrhea during or after therapy. This colitis may range from mild to life threatening in severity.

Mild cases of pseudomembranous colitis may respond to drug discontinuance alone. In more severe cases, management may include sigmoidoscopy, appropriate bacteriological studies, fluid, electrolyte and protein supplementation, and the use of a drug such as oral vancomycin, as indicated. Other causes of colitis should also be considered.

## PRECAUTIONS

**General**

Prolonged use of PRIMAXIN* (imipenem and cilastatin sodium for injection) may result in overgrowth of resistant organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

CNS adverse experiences such as myoclonic activity, confusional states, or seizures have been reported with PRIMAXIN* especially when recommended dosages based on renal function and body weight were exceeded. These experiences have occurred most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) and/or who have compromised renal function. However, there were rare reports in which there was no recognized or documented underlying CNS disorder. Close adherence to recommended dosage schedules is urged especially in patients with known factors that predispose to seizures (see DOSAGE AND ADMINISTRATION). Anticonvulsant therapy should be continued in patients with a known seizure disorder. If focal tremors, myoclonus, or seizures occur, patients should be evaluated neurologically and placed on anticonvulsant therapy if not already instituted. If CNS symptoms continue, the dosage of PRIMAXIN* should be decreased or discontinued.

**Use in Patients with Impaired Renal Function**

Dosage in patients with impaired renal function is based on the severity of infection but the maximum daily dose varies with the degree of renal functional impairment (see DOSAGE AND ADMINISTRATION - Dosage in Patients with Renal Insufficiency).

**Use in Pregnancy**

The use of PRIMAXIN* in pregnant women has not been studied, therefore, PRIMAXIN* should be used during pregnancy only if clearly needed. Use of this drug in women of childbearing potential requires that the anticipated benefits be weighed against possible hazards.

Reproduction studies with bolus I.V. doses suggest an apparent intolerance to PRIMAXIN* (including emesis, inappetence, body weight loss, diarrhea and death) at doses equivalent to the average human dose in pregnant rabbits and cynomolgus monkeys that is not seen in non-pregnant animals in these or other species. In other studies, PRIMAXIN* was well tolerated in equivalent or higher doses (up to 11 times the average human dose) in pregnant rats and mice (see REPRODUCTION STUDIES under TOXICOLOGY in the complete monograph).

**Nursing Mothers**

It is not known whether PRIMAXIN* is excreted in milk. If the use of PRIMAXIN* is deemed essential, the patient should stop nursing.

**Pediatric Use**

Efficacy and tolerability in infants under the age of 3 months have not yet been established; therefore, PRIMAXIN* is not recommended in the pediatric age group below the age of 3 months.

**Drug Interactions**

Concomitant administration of PRIMAXIN* and probenecid results in only minimal increases in plasma levels of imipenem and plasma half-life. It is not recommended that probenecid be given with PRIMAXIN*.

PRIMAXIN* should not be mixed with or physically added to other antibiotics. PRIMAXIN* has been administered concomitantly with some antibiotics, such as aminoglycosides.

There is no evidence to suggest that association of PRIMAXIN* with any other beta-lactam antibiotics has any therapeutic advantage.

## ADVERSE REACTIONS

PRIMAXIN* (imipenem and cilastatin sodium for injection) is generally well tolerated. The following adverse reactions were reported on 1,723 patients treated in clinical trials. Many of these patients were severely ill and had multiple background diseases and physiological impairments, making it difficult to determine causal relationship of adverse experiences to therapy with PRIMAXIN*.

**Local Adverse Reactions**

Adverse local clinical reactions that were reported as possibly, probably or definitely related to therapy with PRIMAXIN* were:

| | Incidence (%) |
|---|---|
| Phlebitis/thrombophlebitis | 1.7 |
| Infused vein pain | 0.6 |
| Vein induration | 0.2 |
| Infused vein infection | 0.1 |

**Systemic Adverse Reactions**

Adverse clinical reactions that were reported as possibly, probably, or definitely related to PRIMAXIN* were:

| | Incidence (%) |
|---|---|
| **Gastrointestinal** | |
| nausea | 2.0 |
| diarrhea | 1.7 |
| vomiting | 1.6 |
| tongue papillar hypertrophy | 0.2 |
| pseudomembranous colitis (see WARNINGS) | 0.1 |
| hemorrhagic colitis | <0.1 |
| gastroenteritis | <0.1 |
| abdominal pain | <0.1 |
| glossitis | <0.1 |
| heartburn | <0.1 |
| pharyngeal pain | <0.1 |
| increased salivation | <0.1 |
| **CNS** | |
| fever | 0.4 |
| dizziness | 0.3 |
| seizures (see PRECAUTIONS) | 0.2 |
| somnolence | 0.2 |
| confusion | 0.2 |
| myoclonus | 0.1 |
| vertigo | 0.1 |
| headache | 0.1 |
| encephalopathy | <0.1 |
| paresthesia | <0.1 |
| **Special Senses** | |
| transient hearing loss in patients with impaired hearing | <0.1 |
| tinnitus | <0.1 |

**Respiratory**

| | |
|---|---|
| dyspnea | 0.1 |
| hyperventilation | <0.1 |
| thoracic spine pain | <0.1 |

**Cardiovascular**

| | |
|---|---|
| hypotension | 0.4 |
| palpitations | 0.1 |
| tachycardia | <0.1 |

**Renal**

| | |
|---|---|
| oliguria/anuria | <0.1 |
| polyuria | <0.1 |

**Skin**

| | |
|---|---|
| rash | 0.9 |
| pruritus | 0.3 |
| urticaria | 0.2 |
| skin texture changes | 0.1 |
| candidiasis | 0.1 |
| erythema multiforme | <0.1 |
| facial edema | <0.1 |
| flushing | <0.1 |
| cyanosis | <0.1 |
| hyperhidrosis | <0.1 |
| pruritus vulvae | <0.1 |

**Body as a whole**

| | |
|---|---|
| polyarthralgia | <0.1 |
| asthenia/weakness | <0.1 |

### Adverse Laboratory Changes

Adverse laboratory changes, without regard to drug relationship, that were reported during clinical trials were:

**Hepatic**: Increased SGPT, SGOT, alkaline phosphatase, bilirubin and LDH.

**Hemic**: Increased eosinophils, positive Coombs test, decreased WBC and neutrophils, increased WBC, increased platelets, decreased platelets, decreased hemoglobin and hematocrit, increased monocytes, abnormal prothrombin time, increased lymphocytes, increased basophils.

**Electrolytes**: Decreased serum sodium, increased potassium, increased chloride.

**Renal**: Increased BUN, creatinine.

**Urinalysis**: Presence of urine protein, urine red blood cells, urine white blood cells, urine casts, urine bilirubin, and urine urobilinogen.

## TREATMENT OF OVERDOSAGE

There are no data available on overdosage.

PRIMAXIN* (imipenem and cilastatin sodium for injection) is cleared by hemodialysis.

## DOSAGE AND ADMINISTRATION

The dosage recommendations for PRIMAXIN* (imipenem and cilastatin sodium for injection) represent the quantity of imipenem to be administered by I.V. infusion only. An equivalent amount of cilastatin is also present in the solution.

The dosage of PRIMAXIN* should be determined by the severity of the infection, renal function, body weight, the antibiotic susceptibility of the causative organism(s) and the condition of the patient. Doses cited are based on body weight of 70 kilos.

The median duration of treatment with PRIMAXIN* in clinical trials for infections of the various body systems ranged from 6 to 10 days except for endocarditis and bone and joint infections for which the median duration of treatment was 4 weeks.

### Dosage in Adults

The recommended daily dose is 1 to 2 g administered in equally divided doses every 6 to 8 hours (see Table 1).

### Dosage in Elderly Patients

The recommended dosage of PRIMAXIN* in elderly patients with normal renal function is the same as given for adults above. Renal status of elderly patients may not be accurately portrayed by measurement of BUN or creatinine alone. Determination of creatinine clearance is suggested to provide guidance for dosing in such patients.

**TABLE 1**

**ADULT DOSAGE OF PRIMAXIN***

| Severity of infection | I.V. Administration: Dose (mg of imipenem) | Dosage Interval | Daily Dose |
|---|---|---|---|
| Mild | 250 mg | 6 h | 1.0 g |
| Moderate | 500 mg | 8 h | 1.5 g |
| Severe (fully susceptible) | 500 mg | 6 h | 2.0 g |
| Severe× infections due to less susceptible organisms or life threatening conditions | 1000 mg<br>1000 mg | 8 h<br>6 h | 3.0 g<br>4.0 g |

× Primarily some strains of *Ps. aeruginosa*.

The maximum daily dose should not exceed 4 g or 50 mg/kg, which ever is less.

### Dosage in Patients with Renal Insufficiency

Patients with creatinine clearances of ≤5 mL/min/1.73 m² (≤0.08 mL/s/1.73 m²) should not receive PRIMAXIN* unless hemodialysis is instituted within 48 hours. Both imipenem and cilastatin are cleared from the circulation during hemodialysis. The patient should receive PRIMAXIN* after hemodialysis and at 12 hour intervals timed from the end of that hemodialysis session. Dialysis patients, especially those with background CNS disease, should be carefully monitored; for patients on hemodialysis, PRIMAXIN* is recommended only when the benefit outweighs the potential risk of seizures (see PRECAUTIONS). Currently, there are inadequate data to recommend the use of PRIMAXIN* in patients undergoing peritoneal dialysis.

**TABLE 2**
**MAXIMUM DOSAGE OF PRIMAXIN* IN RELATION TO RENAL FUNCTION**

| RENAL FUNCTION | CREATININE CLEARANCE mL/min/1.73 m² (mL/s/1.73 m²) | DOSE (g) | DOSAGE INTERVAL (h) | MAXIMUM TOTAL DAILY DOSAGE (g) |
|---|---|---|---|---|
| Mild impairment | 31 - 70 (0.52 - 1.17) | 0.5 | 6 - 8 | 1.5 - 2 |
| Moderate impairment | 21 - 30 (0.35 - 0.50) | 0.5 | 8 - 12 | 1 - 1.5 |
| Severe× impairment | 0 - 20 (0 - 0.33) | 0.25 - 0.5 | 12 | 0.5 - 1.0×× |

× Patients with creatinine clearance of 6 to 20 mL/min/1.73 m² (0.1 - 0.3 mL/s/1.73 m²) should be treated with 250 mg (or 3.5 mg/kg whichever is lower) every 12 hours for most pathogens. When the 500 mg dose is used in these patients, there may be an increased risk of seizures.

×× The highest dose is only recommended for infections due to less susceptible organisms primarily some strains of *Ps. aeruginosa*.

When only the serum creatinine level is available, the following formula (based on sex, weight, and age of the patient) may be used to convert this value into creatinine clearance (mL/min). The serum creatinine should represent a steady state of renal function.

Males:
$$\frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/100 mL)}}$$

Females: 0.85 x above value.

When using the International System of units (SI), the estimated creatinine clearance (mL/s) in males can be calculated as follows:

$$\frac{(\text{lean body weight, kg}) \times (140 - \text{age, years}) \times 1.4736}{(72) \times (\text{serum creatinine concentration, } \mu\text{mol/L})}$$

and in females the estimated creatinine clearance (mL/s) is:

$$\frac{(\text{lean body weight, kg}) \times (140 - \text{age, years}) \times 1.2526}{(72) \times (\text{serum creatinine concentration, } \mu\text{mol/L})}$$

PRIMAXIN* is cleared by hemodialysis. After each dialysis session the dosage schedule should be restarted.

### Dosage in Infants and Children

The recommended total daily dosage of PRIMAXIN* in children and infants 3 months of age and older is 60 to 100 mg/kg of body weight divided into 4 equal doses given at six hour intervals. The higher dosages should be used for infants and young children. The total daily dosage should not exceed 2 grams. Clinical data are insufficient to recommend an optimum dose for infants and children with impaired renal function.

### Administration

**CAUTION**: CONTENTS OF VIALS NOT FOR DIRECT INFUSION.

Each reconstituted 250 mg or 500 mg dose should be given by intravenous infusion over twenty to thirty minutes. Each 1000 mg dose should be infused over 40 to 60 minutes. In patients who develop nausea during the infusion, the rate of infusion may be slowed.

### RECONSTITUTION

Contents of the 13 mL vials must be suspended and transferred to 100 mL of an appropriate infusion solution.

A suggested procedure is to transfer approximately 10 mL from the 100 mL of the appropriate infusion solution to the vial (see list of diluents under COMPATIBILITY AND STABILITY). Shake well. Return the resulting 10 mL of suspension to the remaining 90 mL of the infusion solution.

Repeat, using 10 mL of the diluted suspension, to ensure complete transfer of the contents of the vial to the infusion solution.

**CAUTION:** CONTENTS OF VIALS NOT FOR DIRECT INFUSION.

## COMPATIBILITY AND STABILITY

### List of diluents

0.9% Sodium Chloride Injection
5% or 10% Dextrose Injection
5% Dextrose Injection with 0.02% sodium bicarbonate solution
5% Dextrose and 0.9% Sodium Chloride Injection
5% Dextrose Injection with 0.225% or 0.45% saline solution
NORMOSOL-M in D5-W
5% Dextrose Injection with 0.15% potassium chloride solution
Mannitol 2.5%, 5% and 10%

### Reconstituted solutions

Solutions of PRIMAXIN* range from colourless to yellow. Variations of colour within this range do not affect the potency of the product.

PRIMAXIN*, as supplied in vials and reconstituted as above maintains satisfactory potency for four hours at room temperature and for 24 hours under refrigeration (4°C). PRIMAXIN* has been found to be stable in 0.9% Sodium Chloride Injection for 10 hours at room temperature and 48 hours under refrigeration.

## DOSAGE FORMS

### AVAILABILITY

PRIMAXIN* is supplied as a sterile powder mixture in vials containing imipenem anhydrous and cilastatin sodium as follows:

3514 Ca - 250 mg imipenem equivalent and 250 mg cilastatin equivalent in vials.

3516 Ca - 500 mg imipenem equivalent and 500 mg cilastatin equivalent in vials.

### STORAGE

The dry powder should be stored at a temperature below 30°C.

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# 5. Definitive Surgical Management for Soft-Tissue Sarcomas

H.R. Shibata, MD, FRCSC, FACS

**The surgical management of soft-tissue sarcomas, a seemingly heterogeneous group of malignant tumours, depends on the circumstances (e.g., untreated primary tumour, inadequately resected primary tumour, local recurrence, metastasis) and site.**

**The basic steps in managing a primary tumour include using the correct method to establish a diagnosis, obtaining adequate tumour-free resection margins and giving consideration to adjuvant radiotherapy or chemotherapy, or both. Local recurrences and metastatic lesions require a multidisciplinary approach.**

**The relative rarity of this group of sarcomas and the low survival rate associated with them make it mandatory that such patients be treated in centres able to provide specialized care from the beginning.**

**Le traitement chirurgical des sarcomes des tissus mous, un groupe apparemment hétérogène de tumeurs malignes, dépend des circonstances (qu'il s'agisse d'une tumeur primaire non traitée ou non suffisamment réséquée, d'une récidive locale ou d'une métastase) et du foyer.**

**La marche à suivre dans le traitement d'une tumeur primaire commence par l'utilisation de la méthode diagnostique appropriée, et se poursuit par l'obtention d'une marge de résection exempte de tumeur adéquate en considérant la possibilité d'avoir à utiliser une radiothérapie ou un chimiothérapie d'appoint. Les récidives locales et les métastases exigent une approche multidisciplinaire.**

**La rareté relative de ce groupe de tumeurs et le faible taux de survie qui y est rattaché obligent que les patients qui en sont frappés soient traités dans des centres capables de fournir des soins spécialisés dès le début.**

With increasing knowledge of the biology of soft-tissue sarcomas, their surgical management, as with other human cancers, has slowly evolved from conservative to radical techniques and back to conservative combined with other modalities.

The surgeon's objective in managing patients with soft-tissue sarcomas is cure. Risk factors that are important in determining the outcome in the patient with a soft-tissue sarcoma are: the size of the tumour, site or tissue of origin, and histopathologic grading of the tumour. The smaller the tumour, the better are the chances for margins of resection that are free of tumour and therefore give better overall results. Sarcomas that originate in the extremities, both upper and lower, afford a much better survival rate than those arising in the head and neck, trunk, retroperitoneal space and viscera. The importance of obtaining a good history and physical examination, appropriate laboratory investigations, including angiography, computed tomography and magnetic resonance imaging, and a carefully planned biopsy have already been emphasized. These measures provide information essential in planning the definitive surgical procedure.

## Surgical Treatment

The surgical procedure must be adapted to the circumstances (an untouched primary, inadequately resected primary, local recurrence, metastasis) and site (extremities, trunk, head and neck, retroperitoneal space, viscera) of the tumour.

### *Primary Tumour*

Because local recurrence after simple excision ("shelling out") ranges from 65% to 90%, the goal of the surgeon must be surgical

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resection with tumour-free margins. Although the local recurrence rate may still be as high as 28% to 36% for high-grade lesions, this may be reduced by adjuvant therapy.[1,2]

Soft-tissue sarcomas of the extremities can be managed by four types of resection: local, wide local, compartmental and amputation.

- Local resection is limited to a very small margin of normal tissue. At times, this may be called an excisional biopsy, and, unfortunately, no further local procedure is performed for better local control.
- Wide local resection is the treatment of choice for superficial smaller lesions. Frozen-section examination should be carried out whenever possible at the time of surgery to ensure tumour-free margins.
- Compartmental resection should be used for deeper tumours. This procedure involves removal of all the muscles in the particular compartment containing the tumour, from their origin to insertion. Adequate margins may be obtained easily in a longitudinal axis, but the distance from adjacent bone, nerves and vessels may be quite small and may be the limiting factor.[3]
- Amputation may be necessary when the tumour is large and deep-seated, compromising major vessels, nerves or bone. However, the modern trend is toward limb salvage procedures with adjuvant radiotherapy or chemotherapy.[4] In the pattern of care survey of adult soft-tissue sarcomas carried out by the American College of Surgeons in the United States for the periods 1977 to 1978 and 1983 to 1984, little change was demonstrated in operative procedures; 6.4% and 8.2% of patients underwent primary amputation respectively (Table I).[1]

For tumours in other parts of the body, the relation of the tumour to vital structures will determine how radical the excision must be. Intraoperative biopsy with frozen-section examination may help to achieve tumour-free margins of resection but does not guarantee freedom from local recurrence. However, the 5-year survival figures are approximately 10% better if biopsy proven tumour-free margins are achieved.

Five-year survival rates are closely linked to site, being highest for extremity tumours, intermediate for head and neck and visceral tumours, and lowest for those in the mediastinum or retroperitoneum.

*Inadequately Resected Tumours*

If the sarcoma is superficial or of low grade, or both, further wide local excision may be adequate. However, patients with poorly differentiated sarcomas are at risk for greater local recurrence and dissemination because of previous tissue contamination, and in such patients adjuvant therapy should be considered after further resection.

*Local and Regionally Recurrent Tumours*

Most tumour recurrences occur within 2 years of primary management. Distant metastases from poorly differentiated sarcomas also develop during this time. If there is no evidence of metastatic disease, further resection following the same principles as outlined for primary tumours are appropriate, but adjuvant treatments such as radiotherapy and chemotherapy are highly recommended.

*Metastases*

If metastatic lesions are confined to regional nodes, radical lymphadenectomy is recommended, but the long-term prognosis is poor.[5] Resection of pulmonary metastases in selected patients whose tumour has a slow doubling time may salvage 20% of such patients.[6] Occasionally, resection of other metastatic sites, such as the liver, may be appropriate.

## Combination Therapy

Figure 1 suggests an algorithm that could be followed in the management of soft-tissue sarcomas. After a soft-tissue mass has been diagnosed as a sarcoma by the different methods outlined in the second box, it can be classified into subsets by age, site and stage of disease. The primary resection can then be performed; the possible choices are a radical or a limited local resection. The surgeon should determine whether the margins of resection are free of tumour or involved, because this will influence the postoperative treatment. The grading and localization of the tumour can also be used to subdivide management.

If the tumour is of low grade and localized to the primary site and the margins of resection are adequate,

**Table I** – Type of Surgical Procedures Used in Sarcoma Patients Without Metastases at Time of Diagnosis

| | 1977–1978 | | 1983–1984 | |
|---|---|---|---|---|
| **Procedure** | **No.** | **%** | **No.** | **%** |
| Wide local resection | 879 | 52.4 | 1412 | 56.7 |
| Limited local resection | 455 | 27.1 | 583 | 23.4 |
| Anatomic compartmental resection | 168 | 10.0 | 249 | 10.0 |
| Amputation | 108 | 6.4 | 138 | 5.5 |
| More than one type | 69 | 4.1 | 108 | 4.3 |
| Totals | 1679 | | 2490 | |

then the patient should be followed up carefully with no further therapy. If the margins are inadequate, then repeat resection must be carried out; in this case, postoperative options are radiotherapy or observation. If the tumour is of high grade (poorly differentiated and still localized), radiotherapy must be given postoperatively; following this, adjuvant chemotherapy is optional.

If distant metastases are identified and localized, then surgical resection should be attempted followed by systemic therapy of some type. If the metastases are multiple and multiorgan in nature, then chemotherapy is indicated.

## Discussion

It is interesting that there was very little improvement in the surgical management of soft-tissue sarcomas in North America during two separate 2-year periods (1977 to 1978 and 1983 to 1984) surveyed by the American College of Surgeons. Although their survey did not indicate the reasons for this lack of improvement, it appeared that many North American surgeons did not adhere to the basic principles of good surgical management from the time of surgical diagnosis to local and regional control (Table I).

Because of the rarity of soft-tissue sarcomas, they should ideally be managed at tertiary care centres which can carry out multidisciplinary treatment. The correct techniques for making a surgical diagnosis should be taught in all surgical training programs and the impression made that surgical resection should be performed in the majority of patients by a surgeon with expertise and experience in the field, who also acts as a vital member of the oncology team. Improvement in local control as well as overall survival can only be achieved in this manner.

There is an urgent need to inform practising surgeons of all disciplines involved in the management of this type of cancer that multidisciplinary management and participation in clinical trials are necessary.

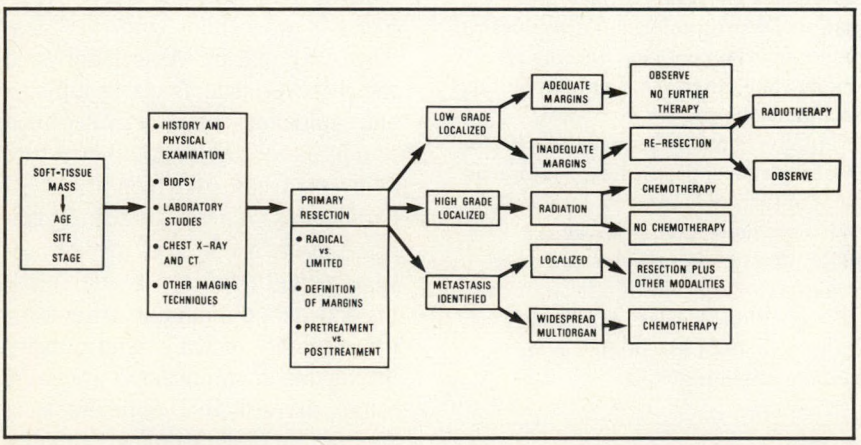


**FIG. 1 — Algorithm for management of soft-tissue sarcomas. CT = computed tomography.**

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# Guidelines for the Surgical Management of Soft-Tissue Sarcoma. Report of the Canadian Sarcoma Group

W.J. Temple, MD, FACS, FRCSC;* V. Bramwell, PhD, MB, BS, FRCPC;† E. Eisenhauer, MD, FRCPC;‡ R.D.T. Jenkin, MB, FRCR, FRCPC;§ F. Langer, MD, FRCSC;¶ A.J. Worth, MD, FRCPC‖

**The Canadian Sarcoma Group was formed in 1985 by interested surgeons, oncologists and pathologists. In the evaluation of new protocols, standard surgical guidelines have been developed which incorporate the concepts of multimodality therapy, particularly radiotherapy and chemotherapy. Also defined are the procedures performed: biopsy, marginal resection, wide local excision, radical resection and the principles to be considered when doing a diagnostic biopsy and a curative resection, particularly with limb salvage in mind. To optimize local control of the disease, centres treating sarcomas should have access to computed tomography, radionuclide scanning, to radiation and medical oncologists, and members of other surgical specialties. This team approach increases survival by 10% and also provides the best circumstances in which to study adjuvant therapy. Surgical guidelines are also essential in order to compare the results of different clinical trials.**

**En 1985, des chirurgiens, oncologues et pathologistes intéressés formèrent le Groupe canadien pour les sarcomes. A l'évaluation des protocoles, des directives chirurgicales standard furent élaborées, lesquelles enveloppent des concepts de thérapie multimodale comprenant radiothérapie et chimiothérapie. Les interventions pratiquées ont aussi été définies: biopsie, résection de marge, excision locale étendue, résection radicale et les principes devant être considérés quand on effectue une biopsie de diagnostic ou une résection à visée curative, particulièrement quand on envisage la conservation d'un membre. Afin d'optimiser le contrôle local de la tumeur, les établissements où l'on traite les sarcomes doivent disposer de la tomodensitométrie, de la scintigraphie isotopique, de radiothérapeutes et d'oncologues, en plus des membres des diverses spécialités chirurgicales. Cette approche d'équipe augmente la survie de 10% et offre des conditions idéales pour étudier les thérapies adjuvantes. Des directives chirurgicales sont aussi essentielles pour pouvoir comparer les résultats de différentes études cliniques.**

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In 1985 the Canadian Sarcoma Group (CSG) was formed by interested general surgeons, orthopedic surgeons, medical oncologists, radiation oncologists and pathologists, supported by the National Cancer Institute of Canada (NCIC) Clinical Trials Group. Its purpose is to develop national protocols and to initiate or participate in international protocols for sarcoma treatment. One essential component of the program is a set of surgical guidelines to assure adequate local treatment. In workshops with the Canadian Orthopaedic Association and the NCIC Clinical Trials Group specific guidelines have been accepted as a basis for any ongoing or future adjuvant trials in which the CSG participates. These guidelines embrace modern concepts of limb salvage surgery for soft-tissue sarcoma and define minimum criteria for the eligibility of patients in primary management multicentre trials. It is our premise that optimum local control not only reduces morbidity but contributes to the overall cure rate in as many as 10% of patients.[1]

A standard set of definitions has been adopted to describe a surgical procedure.

- Biopsy is removal of a portion of the tumour for diagnosis.
- Intralesional resection is excision through the pseudocapsule leaving gross tumour.
- Marginal resection is incomplete excision, when gross and histologically negative tumour margins are present, but the periphery of the

tumour is very close to the resection edge (as close as 1 mm) in one or more planes.

- Wide resection is excision of the tumour and at least one layer of uninvolved fascia or 2 cm gross distance between tumour and resection edge, proven histologically.
- Radical resection is a compartmental excision involving removal of muscle groups from origin to insertion and one fascial plane beyond the tumour.[2]

## Biopsy Technique

All deep or large soft-tissue masses must be considered sarcomas until proven otherwise. They should be approached in two stages — a diagnostic, incisional biopsy followed by therapeutic excision once the diagnosis is determined histologically.[3] The error of doing two operations for a benign soft-tissue lesion is less serious than removing, in one stage, an unsuspected sarcoma without appropriate planning. Poor biopsy planning may result in unnecessary loss of limb.[4]

Physical examination and computed tomography or nuclear magnetic resonance imaging help to localize the tumour and permit the most direct approach to biopsy. A longitudinal incision is preferred to a transverse incision so that the residual scar can be included in the en-bloc excision of the sarcoma. To avoid tumour extension the approach to the lesion should be intra- not intercompartmental. The adequacy of the specimen may be verified by frozen-section examination. If a drain is used, it should be brought through the wound at a site that will be excised en bloc with the tumour. Once a precise diagnosis has been made and the search for metastatic disease completed, the patient can be treated appropriately.

## Definitive Surgery

The prerequisite for successful sarcoma surgery is to obtain a microscopically clear margin around the tumour, through normal tissue, not through or near the reactive pseudocapsule. The fact that megavoltage irradiation can eradicate microscopic residual disease means that margins smaller than those required for radical resection or amputation may be adequate. However, because of the nature of local spread of sarcomas along tissue planes and into unexpected areas, it is useful arbitrarily to define a wide surgical margin: a fascial plane separating the tumour from normal tissue is considered to be the minimum acceptable margin. For the above reasons only basic guidelines for resection of sarcomas can be proposed, and these will change somewhat according to the size of the tumour and its location. When these guidelines are followed, optimal local control rates should be as high as 90%.

Guidelines for definitive surgical resection of sarcoma are as follows:

- When possible a 2-cm margin of normal tissue should be obtained around the sarcoma. When an uninvolved fascial plane intervenes, a margin less than 2 cm is acceptable but the fascial plane must be included in the specimen.
- Using frozen sections, the surgeon must document all margins of resection as being tumour free at the time of surgery. The sections are best taken from the residual tissue defect in the patient rather than from the specimen itself. The closest margin should be checked by at least two samples and the other four margins checked with one sample each. The margins should include deep, lateral, medial, caudad and cephalad sites. If the skin is also infiltrated, frozen sections of its margins should also be obtained. The best sites for biopsy include fascial planes involved by the tumour which are often areas of microscopic extension. Clinical experience has shown that a minimum tissue margin of 2 cm around the gross specimen is associated with the highest chance of a histologically disease-free margin and a low risk of inadvertently exposing the tumour. If the tumour is not removed intact, the chance of local control of disease is thought to be reduced. When larger margins can be achieved without substantially sacrificing limb function, so much the better.
- Intraoperatively, the pathologist and surgeon together should cut the specimen and locate areas where tumour is close to the margins. The corresponding areas in the resection defect should then be checked by frozen-section examination before the operation is completed.
- When the skin is not involved, any previous biopsy or excision scar should be removed with approximately 2 cm of tissue en bloc with the tumour. If the skin is involved, then margins should be larger and frozen-section examination is necessary to confirm the tumour-free margins.
- When an amputation is required, the distance from the tumour to the transection level should be recorded if the sarcoma is in the same limb segment; this also applies to disarticulation. When the amputation is performed more than one joint above the tumour, then the distance to the tumour need not be recorded.
- Metal clips should be placed in the margins of excision, because many of these patients will require adjuvant radiotherapy postoperatively.
- These guidelines for sarcomas apply to local excisions, marginal excisions, compartmental excisions

and high- and low-grade tumours when adjuvant radiotherapy is used. In low-grade lesions not requiring pre- or postoperative radiation, a wide margin of healthy tissue is essential to reduce the risk of local recurrence.

- Radiotherapy may be used preoperatively to assist limb salvage procedures, facilitating dissection of the tumour from adjacent major structures, especially for high-grade or large sarcomas.
- After resection of high-grade or large sarcomas by wide local excision or amputation in the same limb segment, postoperative radiation is advisable.
- These guidelines are applicable not only to limb sarcomas but also to head and neck, trunk and chest wall sarcomas and retroperitoneal sarcomas.


## Summary

Optimal primary sarcoma surgery usually takes place in a tertiary care facility where access to computed tomography, angiography and a staff of neurosurgeons, vascular and plastic surgeons, medical oncologists, radiation oncologists, pathologists and physiotherapists are available to support the primary orthopedic or general surgeon. Optimal local control rates should be 80% to 90% when these specific guidelines are followed. We expect the implementation of these guidelines in limb salvage surgery will reduce the morbidity and mortality associated with local recurrence of the sarcoma. The true value of adjuvant local or systemic treatments such as radiotherapy or chemotherapy may then be accurately determined. We hope that the majority of sarcoma patients will be treated in the context of prospective trials by experienced teams acquiring information and thereby improving the rate of cure.


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## BOOK REVIEWS

*continued from page 384*

leading. For example, there is a valuable chapter on renal masses, which contains an excellent discussion of renal cysts. However, in dealing with solid renal masses, the value of ultrasonography is underemphasized. In my clinical experience, ultrasonography is the most valuable aid for screening and diagnosing solid renal masses, yet the author tends to downplay its role as compared with intravenous pyelography and computed tomography. There are some minor criticisms of the book's organization and content. The long chapter on the malfunctioning kidney tends to be repetitive and dull, since there are very few diagnostic features to differentiate the many intrinsic renal diseases. The chapter on prostate ultrasonography is slightly outdated owing to the rapid advances made in the last 2 years. The machines available now produce much better images than those presented in this book and also allow for very accurate transrectal (as opposed to transperineal) biopsy techniques which are not discussed in this text.

Two of the more interesting chapters are those on interventional ultrasonography and ultrasonography of the fetal genitourinary system. As well as being thorough and accurate, these chapters make fascinating reading.

This is an excellent atlas (not a textbook) of genitourinary ultrasound imaging. As well as being a reference aid for the ultrasonographer, it is also an excellent learning tool for the nonradiologist who is involved in the diagnosis and treatment of genitourinary disease.


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**GROWTH FACTORS AND OTHER ASPECTS OF WOUND HEALING. BIOLOGICAL AND CLINICAL IMPLICATIONS. Edited by Adrian Barbul, Eli Pines, Michael Caldwell and Thomas K. Hunt. 342 pp. Illust. Alan R. Liss, Inc., New York, 1988. $68.00. ISBN 0-8451-5116-9.**

This book presents concise and informative chapters on the proceedings of the second international symposium of tissue repair, held at the Innisbrook Resort, Tarpon Springs, Florida in May 1987; the symposium brought together world-class researchers in this field. The editors are leaders in the field of wound repair and wound healing and they report the results of the researchers consistently and extensively. The book's format of grouping together the

*continued on page 440*

# Unusual Gastric Foreign Body: a Case Report

William M. Kuzon, Jr., MD, MSc; Craig A. McFadyen, MD; Frederick L. Moffat, MD, FRCSC

**Ingestion of foreign bodies, either intentionally or accidentally, is quite common. The authors report an unusual case in which a 32-year-old man deliberately assembled a large metallic aggregate in his stomach by swallowing magnets and coins in order to relieve epigastric discomfort. The collection was retrieved by laparotomy and gastrotomy; a gastric ulcer was also found and it was oversewn. Management of this patient is discussed and the principles of treatment for ingested foreign bodies are reviewed.**

**L'ingestion intentionnelle ou accidentelle de corps étrangers est assez fréquente. Les auteurs signalent un cas étrange, celui d'un homme de 32 ans qui, délibérément, assembla dans son estomac un important aggrégat métallique par l'absorption d'aimants et de pièces de monnaie. Cet assemblage fut retiré par laparotomie et gastrotomie; un ulcère gastrique fut également découvert et suturé. Le traitement de ce patient est commenté et les principes de traitement lors de l'ingestion de corps étrangers sont passés en revue.**

Deliberate or accidental ingestion of foreign bodies is relatively common, and there have been numerous reports[1-5] of strange and bizarre objects that have found their way into the gastrointestinal tract. We describe the case of a man who deliberately accumulated a large metallic mass in his stomach by swallowing magnets and coins; ultimately he required surgery to remove the mass.

## Case Report

A 32-year-old man was seen in the emergency department complaining of epigastric discomfort. He said he had been ingesting foreign material for over 2 years to remedy the vague pain. He had a known history of psychiatric illness, which included two suicide attempts (drug overdoses), and was considered to have a schizoid-type personality. Initially, his self-administered treatment relieved his pain, but with time the "therapy" became less effective, and he was again troubled by nondescript upper abdominal discomfort. He had noted the passage of coins in his stool.

About 5 months before he presented at our hospital, he began to swallow small magnets in addition to coins, believing that if he could retain the coins in his stomach longer, they would "do more good". His abdominal pain persisted and he sought medical attention because the magnets and coins had not passed in his stool.

There was no history of gastrointestinal bleeding or of obstructive symptoms. His abdominal pain was epigastric in location, moderate in intensity and was relieved somewhat by meals. He could feel a heavy mass in his abdomen which shifted with changes in position.

He was an asthenic young man. He wore an excessive amount of jewellery; both forearms were entirely covered by metal bracelets of various types and he wore over 50 necklaces. The areolae of both breasts had been pierced and held metal ringlets.

On abdominal examination there was a large, firm, mobile mass in the left upper quadrant; it was best palpated in the epigastrium with the patient on his hands and knees. There was no abdominal distension or tenderness and no other abnormal physical signs.

Routine laboratory investigations gave normal results; hemoglobin concentration 158 g/L and serum amylase 162 U/L (normal range from 0 to 400 U/L).

X-ray films with the patient supine showed a large, irregular, radiopaque mass in the right upper quadrant; with the patient in the

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left lateral decubitus position the mass was shown in the left lower quadrant (Fig. 1).

Flexible esophagogastroduodenoscopy performed the day after admission to hospital revealed a conglomerate of small magnets and coins in the stomach. Superficial gastric erosions were also noted, but the entire stomach was not visualized due to the size of the collection. Attempts to fragment the mass with the endoscope were unsuccessful. The esophagus and duodenum appeared normal.

At laparotomy, the stomach, pylorus and duodenum appeared normal. Through a mid-body gastrotomy the mass of coins and magnets was removed from the stomach (Fig. 2).

A careful inspection of the gastric mucosa, pylorus and duodenum revealed a small gastric ulcer, approximately 1.0 cm in diameter, on the lesser curve 4.0 cm proximal to the cardiac incisure of the stomach. The ulcer had a fibrinous base suggesting chronicity. The overlying serosa was normal. The ulcer was excised down to the deep layers of the muscularis mucosae and the resulting partial thickness defect closed with 2-0 silk sutures. Microscopic examination of the ulcer revealed no evidence of malignant disease.

The patient recovered without complications and was discharged from hospital on postoperative day 7, taking ranitidine for his gastric ulcer. He is currently undergoing psychiatric treatment.

The mass removed from the patient's stomach weighed 585 g and contained 66 Canadian nickels, 23 button magnets (2 cm in diameter and 0.5 cm in length), 2 cylindrical magnets (1 cm diameter and 2 cm in length), 2 iron spheres (1 cm diameter), 1 small square magnet (1 × 0.5 cm) and 12 irregular iron fragments of various sizes and shapes (Fig. 3). Some of the irregular fragments were pieces of larger magnets that had been broken up.

## Discussion

The management of ingested foreign bodies relates to the type of patient, the nature and size of the objects, their location in the gastrointestinal tract and the presence or absence of complications. Several authors[6–8] have presented algorithms useful in the management of these patients.

The problem is usually found in children, psychiatric patients, mentally impaired persons, prisoners, drug and alcohol abusers, denture wearers, or those engaged in certain occupations.[2,4,9–11] In children and workers in particular occupations, the object is usually swallowed accidentally when placed in the mouth during play or work. In substance abusers and those wearing dentures, diminished palatal sensation or gag reflex may contribute to the accidental ingestion. In prisoners, mentally retarded individuals or psychiatric patients, foreign bodies may be swallowed deliberately and repeatedly.[2,11]

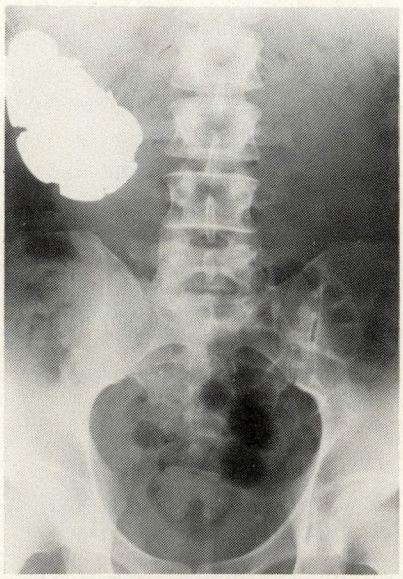

**FIG. 1 — Supine plain film showing large, multisurfaced, radiopaque mass in right upper quadrant.**

The nature of the ingested object is important in determining the appropriate management. Sharp objects may perforate the gut; large objects or conglomerations can cause intestinal obstruction.[7,12,13] The object itself may be corrosive or contain toxic substances, making immediate removal mandatory.[8,11,14] Usually, small blunt objects, such as the coins ingested by our patient, can be managed conservatively, especially if they have reached the stomach.[7,11]

There is general agreement that any object lodged in the pharynx or esophagus must be removed urgently[6,7,15–17] because complications associated with foreign-body impaction above the diaphragm are serious. The complications include airway obstruction or pulmonary aspiration, esophageal perforation, mediastinitis, esophageal obstruction,

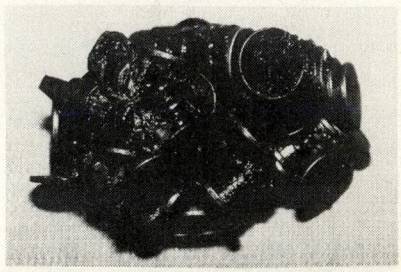

**FIG. 2 — Conglomerate of small magnets and Canadian nickels removed from stomach by gastrotomy.**

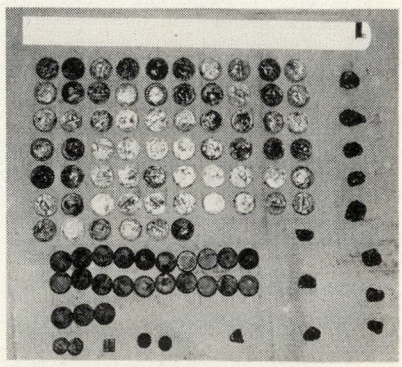

**FIG. 3 — Individual components of mass.**

and, rarely, aortoesophageal fistula.[6,10,16,18-20] Objects usually become lodged in the esophagus at the three anatomic points of narrowing: the cricopharyngeal muscle, the aortic impression or the gastroesophageal junction.[6,16] Carcinoma or strictures of the esophagus predispose to impaction of foreign bodies, especially in cases of the food bolus "cafe coronary".[6,10,16] Although the use of papain to digest a meat bolus is no longer recommended, in some cases relaxation of the smooth muscle of the esophagus using intravenous glucagon and sedation can cause the object to pass into the stomach.[6] Blunt objects at this level can be removed endoscopically[3,6,10,16] or with a Foley catheter.[21] Metallic objects may sometimes be removed using a magnet mounted in the end of a nasogastric tube.[8] Sharp objects generally require endoscopic removal; surgery is rarely necessary.[3,6,10,16] Using an endoscope, the object may be pushed into the stomach in order to turn it around before extraction or in the hope it will eventually pass in the feces.[6]

If the foreign body has reached the stomach, as in our patient, small- or medium-sized objects, even sharp ones, usually will be evacuated without complication in 80% to 90% of cases.[6,7,11] However, obstruction, ulceration, pressure necrosis, perforation, steatorrhea, protein-losing enteropathy, gastrointestinal bleeding, diarrhea and obstructive jaundice have all been described.[1,3,6,9,12,13,22] In specific circumstances, including symptoms of pain, fever, obstruction, jaundice, persistent diarrhea and bleeding,[7,9,12,15,22] removal of a foreign body from the stomach or gut is warranted. Long, slender objects should be removed from the stomachs of children under 2 years of age due to the high incidence of duodenal impaction and perforation.[15] Pre-existing disease, such as pyloric stenosis, is also a relative contraindication to a conservative approach.[23] If the object is in the stomach or proximal duodenum, an attempt at endoscopic removal is recommended,[3,6,10,16] but if the object is located more distally and is producing symptoms, laparotomy is required.

The management of asymptomatic retained foreign bodies in otherwise healthy adults is more controversial. Aboral progress may be arrested at the pylorus, duodenal sweep, ligament of Treitz, ileocecal valve, appendix, sigmoid or rectosigmoid colon.[13,22] Some reports[1,7] recommend intervention if the object is within reach of the endoscope or if x-ray films indicate that impaction has occurred or is likely to occur because of the object's size. Others[2,11] prefer a conservative approach. Since it is difficult to assess the likelihood of complications associated with foreign-body ingestion, management decisions in asymptomatic patients will likely remain controversial.

Our patient had a personality disorder and displayed a tendency toward self-mutilation, both of which are characteristic of individuals who repeatedly swallow foreign objects.[2] However, his motivation was quite lucid and most unusual in that he consciously produced his bezoar for the purpose of treating abdominal symptoms. The result was a large, blunt, gastric conglomeration of magnets and nickels (which are magnetic). Although there was no evidence of bleeding or obstruction, laparotomy was indicated because of the size of the mass and his abdominal pain. In retrospect, it cannot be determined with certainty whether the gastric ulcer was the cause of his original symptoms or secondary to the mass. Therefore, removal of the mass with partial thickness excision since this was a gastric foreign body, a more aggressive attempt to dislodge and remove the components of the mass endoscopically should have been attempted first. As mentioned, the first gastroscopic examination indicated that this would not likely succeed, so a laparotomy was judged to be safer. Vagotomy and pyloroplasty were considered when the ulcer was found, but because of known surgical complications of this procedure, and since the ulcer would likely respond to medical management we elected not to perform a gastric resection or an acid-reducing procedure once intraoperative frozen-section examination had ruled out neoplasia.

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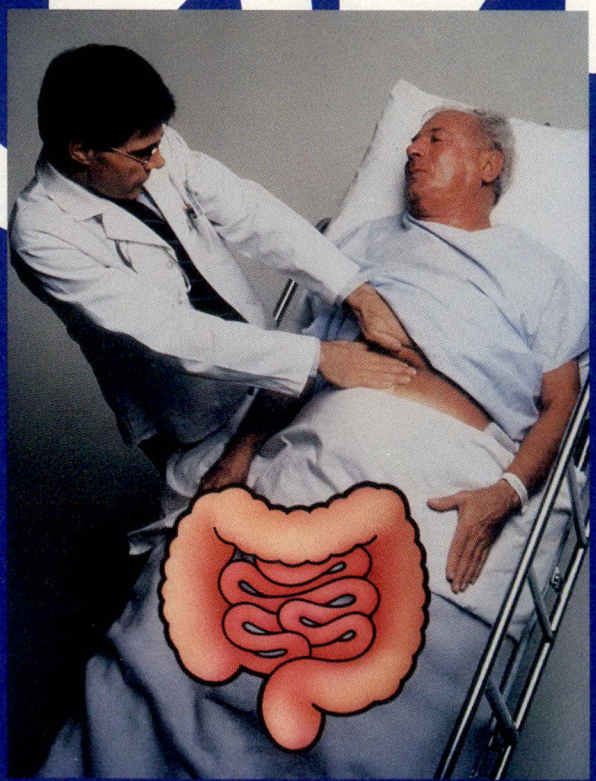

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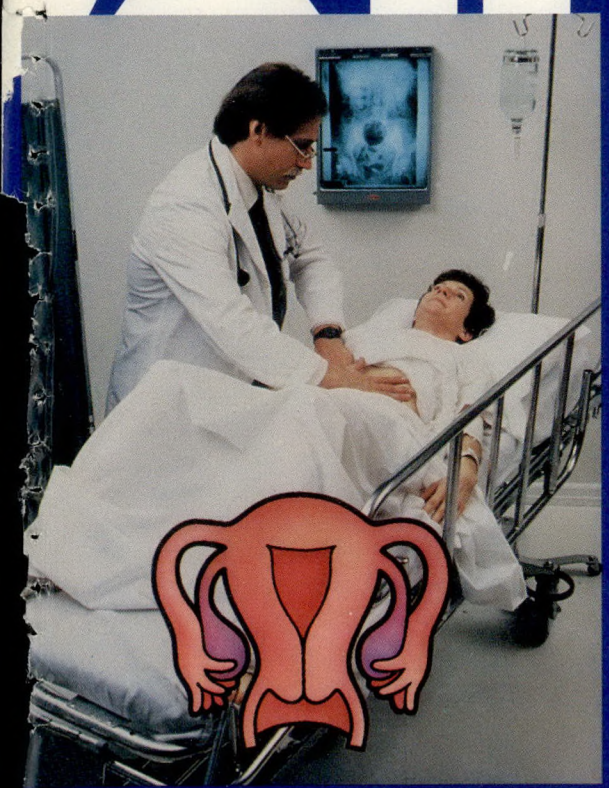

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# Uterine Leiomyosarcoma With Cardiac Metastases

Fredrick Hoy, MD, FRCSC; Robert Boucher, MD; Anthony Brody, MD, FACS

**Leiomyosarcoma metastatic to the heart is rare and is usually fatal. The authors present the case of a 58-year-old woman who had a history of uterine leiomyosarcoma. Echocardiography and cardiac catheterization revealed a large right ventricular mass. Computed tomography confirmed the presence of the mass which extended into the pulmonary artery. The inferior vena cava was free of disease. At operation, a large tumour originating in the right ventricle and protruding through the pulmonary valve was found. Histologically, it was a leiomyosarcoma. Because there were numerous septal and intramural foci of tumour, complete resection was impossible, but palliative resection was performed successfully and the patient was alive and active 1 year after operation.**

**Les léiomyosarcomes avec métastases cardiaques sont rares et habituellement fatals. Les auteurs décrivent le cas d'une femme de 58 ans ayant des antécédents de léiomyosarcome utérin. Une échocardiographie et un cathétérisme cardiaque révélèrent une importante masse au ventricule droit. La tomodensitométrie confirma la présence de cette masse qui s'étendait jusqu'à l'artère pulmonaire. La veine cave inférieure n'était pas touchée. A l'opération, on découvrit une grosse tumeur partant du ventricule droit et faisant saillie à travers la valvule pulmonaire. A l'histologie, on identifia un léiomyosarcome. Comme il y avait plusieurs foyers tumoraux sur et à l'intérieur de la paroi, il fut impossible d'effectuer une résection complète. Une résection palliative fut pratiquée et la patiente était toujours vivante et active un an après l'opération.**

Leiomyosarcoma is a common primary malignant lesion of the heart, but metastatic to the heart it is a rare, highly invasive and usually fatal lesion. A review of the literature revealed only four detailed reports of uterine leiomyosarcoma metastatic to the heart. We present a fifth, but only the third to report an antemortem diagnosis and surgical palliation.

## Case Report

A 58-year-old woman was admitted to hospital complaining of exertional dyspnea that had developed 3 days earlier. Six months before, she had undergone total abdominal hysterectomy and bilateral salpingo-oophorectomy for a stage III poorly differentiated uterine leiomyosarcoma with metastases to the right ovary. Whole lung tomography at that time revealed two nodules, each less than 1 cm in diameter, in the left lung, believed to represent metastatic disease. Postoperatively, the patient had received chemotherapy with doxorubicin.

On examination, the woman was mildly tachypneic. There was a grade III/VI systolic murmur heard diffusely along the right sternal border. Her chest film showed no evidence of congestive heart failure. 2D echocardiography demonstrated a large mass attached to the right ventricular free wall. Cardiac catheterization revealed a mean right atrial pressure of 16 mm Hg and a right ventricular pressure of 70/20 mm Hg. A large filling defect occupied most of the right ventricle (Fig. 1), extending through the pulmonary valve. In addition, there was a filling defect in the right atrium. Computed tomography (Figs. 2 and 3) confirmed these findings. Leiomyosarcoma metastatic to the heart was diagnosed and a palliative tumour resection was undertaken.

The right ventricle was markedly enlarged and a firm mass occupied the chamber of the entire right ventricle, the right ventricular outflow tract and extended into the pulmonary artery. Under cardioplegic arrest, the right atrium was incised and an organized thrombus removed from the appendage. No tumour was present. The pulmonary artery was then opened longitudinally revealing a large friable mucoid tumour protruding through

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the pulmonary valve. When the right ventricle was opened a tumour was found occupying most of the right ventricular chamber and was densely adherent to the septal, anterior and inferior aspects. Multiple septal and intramural areas of tumour foci made complete resection impossible, but the major portion of the tumour mass was excised. A large organized thrombus was also removed from the right ventricle. The patient recovered without complications. The central venous pressure decreased to 8 cm $H_2O$ from 16 cm $H_2O$ and her symptoms were alleviated. She was discharged 8 days postoperatively.

**FIG. 1 — Ventriculogram demonstrates filling defect in right ventricle.**

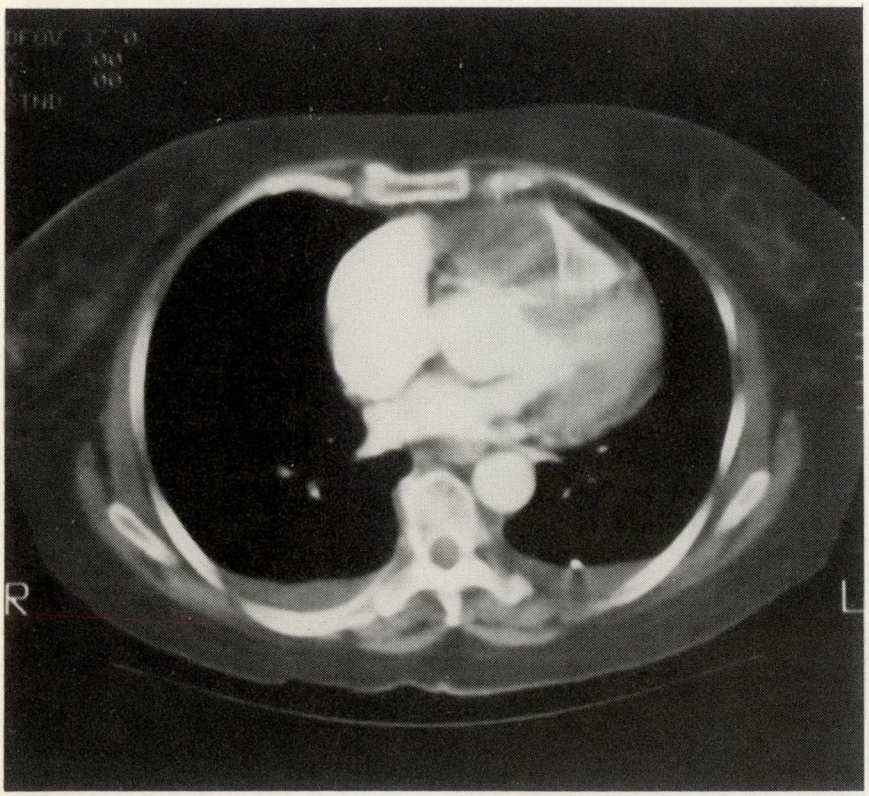


**FIG. 2 — Contrast computed tomogram of thorax shows filling defect in right atrium and right ventricle.**

She was started on a second course of chemotherapy but tolerated this poorly. Five months postoperatively, she had some recurrence of dyspnea and peripheral edema. A 2D echocardiogram showed recurrence of the tumour or thrombus in the right ventricle. She is alive and moderately active 1 year after the palliative resection.

*Pathological Features*

Specimens removed at operation were friable, gelatinous, myxoid masses with multifocal areas of hemorrhage. Fragments of myocardium adherent to the tumour revealed extensive necrosis and infiltration by a malignant neoplasm showing large pleomorphic nuclei and numerous mitotic figures consistent with metastatic leiomyosarcoma.

## Discussion

Cardiac metastases occur in 5% to 20% of patients who die of malignant disease.[1] Secondary cardiac tumours are 16 to 50 times more common than primary ones;[2] 75% to 90% of them arise from tumours of the breast, bronchus, lymphoid tissue or skin. These secondary tumours are rarely the sole metastases[3] and are symptomatic in 15% to 30% of patients.[1]

Sarcomas metastasize to the heart more frequently than carcinomas.[2] Cardiac metastases from leiomyosarcomas of the uterus are extremely rare — 6 out of 2600

patients in one series.[4] Most neoplastic lesions of the heart are silent; symptoms result from impingement on adjacent structures and include arrhythmias, conduction disturbances, effusion, embolism, valve dysfunction, angina, obstruction of blood flow and congestive heart failure. Cardiac dysfunction in a patient with a known neoplasm should arouse suspicion of a cardiac metastasis. Survival from the onset of symptoms is usually short.[2] Of patients whose cardiac involvement is symptomatic, 80% die of cardiac complications.[3]

Uterine leiomyosarcomas are rare, constituting less than 3% of all tumours, and are associated with an incidence of 0.6 per 100 000 females.[5] Metastases are usually to liver and lung. Cardiac metastases from leiomyosarcomas of the uterus are extremely rare, only 6 out of 2600 cases being reported in one series.[4] A review of the literature revealed only four other cases in which clinical data were available. Symptoms developed 1 to 12 years after resection of the uterine leiomyosarcoma. Two patients died before a diagnosis was made.[4,6] Both had large tumour masses originating in the right ventricle. In one who underwent surgery for pericardial effusion, a tumour mass attached to the myocardium by a pedicle 2 cm in diameter was found arising from the surface of the right ventricular outflow tract. This was resected with a large disk of right ventricular wall and the patient was well 15 months postoperatively.[7] Diagnosis of an intracardiac tumour was made preoperatively in the fourth patient. She underwent palliative resection of the right ventricular tumour, but died of low cardiac output 48 hours postoperatively.[8] The diagnosis and operative management of our patient were aided by the use of 2D echocardiography and computed tomography. The patient's symptoms were caused by low right-sided cardiac output due to obstruction of blood flow by the tumour mass and by thrombus secondary to stasis. The tumour interdigitated with the tricuspid valve and trabeculae of the right ventricle so that only palliative resection could be performed. Postoperatively, the mean central venous pressure decreased markedly and the patient was symptomatically much improved. The highly malignant nature of her tumour is attested to by the disappointing early return of symptoms and recurrence of tumour. Cardiac symptoms in patients with known metastasis should suggest the possibility of an intracardiac metastasis. Since the survival from the onset of symptoms is usually short, palliative resection is justified. The diagnosis can be greatly aided by noninvasive techniques and prolonged symptom-free survival may be obtained in patients with tumours of lower-grade malignancy or those that are more responsive to chemotherapy or radiotherapy.

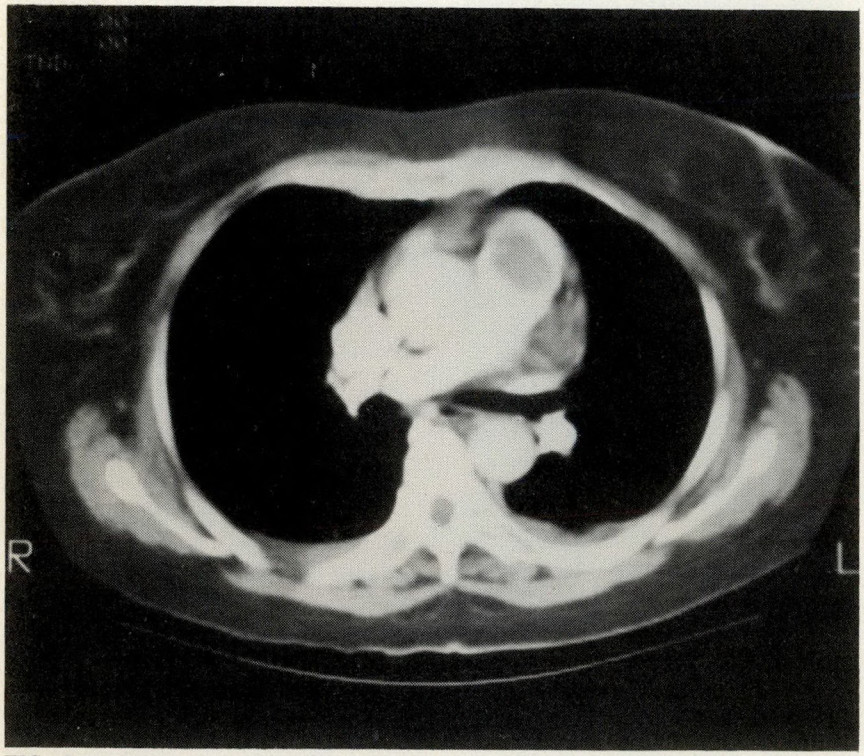


**FIG. 3 — Contrast computed tomogram of thorax demonstrates filling defect in pulmonary artery.**

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# Normoglycemia After Implantation of Purified Islet Cells in Dogs

G.L. Warnock, MD, MSc, FRCSC;* M.S. Cattral, MD;* R.V. Rajotte, BSc, MSc, PEng, PhD†

**A major problem that limits the effectiveness of clinical trials of islet transplantation is the inability to isolate sufficient pure viable islets from a single pancreas. The authors have evaluated this problem, using dogs rendered diabetic by total pancreatectomy. An average of $123 \pm 11 \times 10^3$ highly purified islets (mean graft weight $0.75 \pm 0.1$ g) were implanted as splenic allografts (seven dogs), splenic autografts (six dogs) or liver autografts (six). In the autograft recipients, fasting normoglycemia was maintained during follow-up to 10 months; onset of hyperglycemia was delayed in three liver recipients and one splenic autograft recipient at 1.5, 2, 8 and 10 months respectively. The K values (decline in glucose levels in %/min) during intravenous glucose tolerance testing were more than 1.0. Six recipients of allografts and cyclosporine (CsA) were normoglycemic when CsA trough serum levels were greater than 300 $\mu$g/L, although the fasting plasma glucose level was higher than that in autograft recipients. These data show that purified islets isolated from a large mammal will maintain fasting normoglycemia for prolonged periods after auto- or alloimplantation.**

**Un problème majeur limite l'efficacité des essais cliniques de greffes d'îlots de Langerhans, soit l'incapacité d'isoler suffisamment d'îlots purs et viables d'un seul pancréas. Les auteurs ont étudié ce problème chez des chiens rendus diabétiques par pancréatectomie totale. Une moyenne de $123 \pm 11 \times 10^3$ îlots hautement purifiés (poids moyen de la greffe: $0.75 \pm 0.1$ g) ont été greffés sous forme d'allogreffes spléniques (sept chiens), d'autogreffes spléniques (six chiens) ou d'autogreffes hépatiques (six chiens). Chez les receveurs d'autogreffes, une normoglycémie à jeun s'est maintenue durant une période de contrôle de 10 mois; une hyperglycémie d'apparition retardée est survenue chez trois receveurs de greffes hépatiques et chez un receveur d'autogreffe splénique après, respectivement, 1.5, 2, 8 et 10 mois. Les valeurs de K (la baisse de la glycémie en %/min) durant les épreuves d'hyperglycémie provoquée par voie intraveineuse ont toutes été supérieures à 1.0. Six porteurs d'allogreffes, qui recevaient de la cyclosporine (CsA), sont demeurés normoglycémiques alors que les concentrations plasmatiques minimums de CsA étaient inférieures à 300 $\mu$g/L, bien que leur glycémie à jeun ait été supérieure à celle des receveurs d'autogreffes. Ces données démontrent que des îlots purifiés, prélevés chez un grand mammifère peuvent maintenir une normoglycémie à jeun pendant une période prolongée après une auto- ou une allogreffe.**

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Fifteen years have elapsed since the initial report[1] of a cure for experimentally induced diabetes in rodents by implanting free grafts of insulin-producing tissue. Further studies[2] showed that islet cell transplantation prevents or reverses the complications of diabetes mellitus. These procedures have been less successful in large mammals and humans, casting doubts on their feasibility. As with other organ grafts, islet allografts are subject to rejection, but a major problem has been the inability to isolate sufficient pure, viable islet cells from a single pancreas. Although the yield can be increased by collecting islet-containing pancreatic microfragments,[3] their implantation results in severe portal hypertension.[4]

Recent advances in islet cell isolation suggest that a technique may soon be available for clinical trials. Alejandro and colleagues[5] isolated sufficient purified islets to reverse diabetes in pancreatectomized dogs; however, delayed graft failures occurred, suggesting that a marginally adequate islet mass had failed. We have combined the methods of collagenase perfusion by way of the ducts,[6] gentle trituration of tissue[7] and density gradient centrifugation[8] to separate purified islets from the canine pancreas. Our studies showed that more than 5000 islets/kg body weight (average endocrine particle size 122 $\mu$m) consistently induced normoglycemia.[9] In this study, we subjected these highly purified grafts to prolonged follow-up and evaluated the effects of allograft implantation and cyclosporine (CsA) immunosuppression.

## Materials and Methods

*Pancreatectomy*

Under general anesthesia with sodium pentobarbital (30 mg/kg body weight), the pancreas in 29 adult mongrel dogs (weight range from 13 to 25 kg) was mobilized. The major vascular connections were preserved until just before excision. Cannulas (20 gauge) were inserted into both main branches of the pancreatic duct and into the left duct by a cutdown 5 cm from the tip of the gland. After excision of the pancreas the abdomen was closed in three dogs (controls), the seven dogs that provided islets for allografts were subjected to euthanasia while under anesthesia and the remaining 19 dogs were maintained under general anesthesia while the islets were being prepared for implantation (about 3 hours).

*Islet Isolation*

The cannulas were perfused (300 mm Hg) with Hanks' solution (Gibco, Chagrin Falls, Ohio) at 4°C for 10 minutes. The perfusate was then changed to a solution of collagenase (type XI or V; Sigma Chemical Co., St. Louis, Miss.) at a concentration of 1600 U/ml in Hanks' solution at 37°C. For six isolations, the collagenase solution (1100 U/ml) was perfused immediately after excision of the pancreas, without preliminary flushing with Hanks' solution. Perfusion was continued at 37°C until the gland became mucoid (25 minutes for type V, 12 minutes for type XI collagenase). The digested tissue was dissociated by teasing and trituration,[7] weighed and resuspended at 4°C to a total volume of 120 ml in Medium-199 with 25 mmol/L Hepes (Gibco, Chagrin Falls, Ohio), 10% fetal calf serum (vol/vol, Gibco, Grand Island, NY), penicillin 100 U/ml and streptomycin 100 μg/ml. Aliquots of 4 ml were removed to 50-ml tubes, suspended in a mixture of 4.3 ml of 5× Medium-199 and 16.7 ml of Ficoll (density 1.125, Sigma) and overlaid with 5 ml each of Ficoll with densities of 1.085, 1.075 and 1.045.[5] The tubes were centrifuged at 550 × *g* for 25 minutes at 22°C. Tissue was collected from the interface of the 1.045/1.075 and 1.075/1.085 layers, washed, recombined, weighed and resuspended to a final volume of 30 ml in culture medium.

*Islet Counts and Size*

Ten samples, each containing 20 μL of freshly-isolated islets, were placed on a microscope slide and protected with a coverslip. Slides were viewed through a stereomicroscope at 25× magnification with side illumination from a fiberoptic light source; islets were identified by their rounded shape, opalescent blue colour and finely granular texture. Islets and islet fragments more than 60 μm in greatest dimension were counted, and the total was estimated from the sample mean. An additional aliquot was examined without a coverslip; the greater and lesser diameter of 10 randomly selected islets of minimum size 60 μm was measured with a graticule and the average islet diameter determined. Purity was estimated by comparing the ratio by volume of islet to exocrine tissue.

*Implantation*

In each case of autografting, the suspended purified islets from the pancreas were either refluxed into the splenic veins (six dogs, group 1) or embolized by way of the portal vein to the liver (six dogs, group 2). Portal venous pressure was measured by connecting the infusion catheter to a manometer before and immediately after infusion of the islets. Postoperatively exocrine enzyme supplements (12 capsules) of Cotazym (Organon Canada Ltd., Montreal, PQ) were provided daily for all 19 dogs. Recipients of splenic allografts (seven dogs, group 3) received CsA (Sandoz Pharmaceutical Co., Basle, Switzerland) intramuscularly daily; the initial daily dose of 20 mg/kg was tapered to 5 mg/kg.

*Blood Indices*

Blood samples were taken preoperatively, postoperatively during glucose tolerance testing, then daily postoperatively for 1 week and subsequently once a week for the duration of follow-up. Fasting plasma glucose (mg/dl) was measured with a Beckman 2 analyser (glucose oxidase; Beckman Instruments, Fullerton, Calif.). The level of immunoreactive insulin (IRI, mU/L) was determined by double-antibody radioimmunoassay,[10] using Pharmacia RIA kits and human insulin standards (Pharmacia, Uppsala, Sweden). For glucose tolerance testing, saphenous veins were cannulated, glucose (0.5 g/kg body weight) was injected intravenously and blood was collected at 0, 1, 5, 10, 15, 30, 60 and 90 minutes for assay of glucose. The K value (decline in glucose level [%/min]) was determined from glucose levels at 5, 10, 15 and 30 minutes.[11] Glucose tolerance testing was repeated at 1 and 3 months in normoglycemic recipients. Trough levels of CsA were measured daily by radioimmunoassay.

*Data Analysis*

Numbers of islets per kilogram implanted, plasma glucose levels and K values for dogs that received liver and splenic autografts were compared using Student's *t*-test for

paired data. The values of plasma glucose in splenic autografts versus allografts were compared using Student's *t*-test for unpaired data. Values were considered significant at $p < 0.05$.

## Results

### *Grafts*

The mean tissue weight after purification with Ficoll was 0.75 ± 0.1 g (±SD). An average of 123 ± 11 × $10^3$ (range from 78 to 188 × $10^3$) islets and islet fragments were recovered per pancreas. Most of the islets were completely free of attached exocrine cells and the average diameter was 122 ± 5 μm (range from 60 to 240 μm). By estimating the relative amount of islet to nonislet tissue, the islets appeared to be 80% to 90% pure.

### *Autografts*

The number of islets administered into the liver (4763 ± 537/kg [±SD]) was similar to that for the spleen (5446 ± 689, $p > 0.05$). After infusion of islets into the portal vein the mean increase in portal pressure was 3.7 ± 0.9 cm $H_2O$; the pressure returned to baseline values within 10 minutes. All recipients maintained their preoperative weight. These dogs became normoglycemic immediately after implantation (Fig. 1) and normoglycemia was maintained at 1 month; plasma glucose values were then 89 ± 6 mg/dl in group 1 and 85 ± 3 mg/dl in group 2 ($p > 0.05$). Delayed failures in graft function occurred in three group 2 dogs at 1.5, 2 and 8 months respectively and a single graft failed in group 1 at 10 months after implantation. The remaining dogs continue to be normoglycemic. To prove conclusively that endocrine function was provided by the graft in the splenic site, two group 1 dogs were subjected to splenectomy; the insulin level in the splenic vein was 20 ± 4 mU/L versus 4 ± 1 mU/L in the artery. Hyperglycemia ensued rapidly after splenectomy. Postoperatively, the K value declined from 3.6 to 1.8 at 1 month in group 1 (Fig. 2a) and from 3.9 to 1.6 in group 2 (Fig. 2b), but had not declined significantly more at 1.7 and 1.4 respectively after 3 months. The insulin levels were reduced in all dogs postoperatively and the peak response was delayed after islet implantation into the spleen.

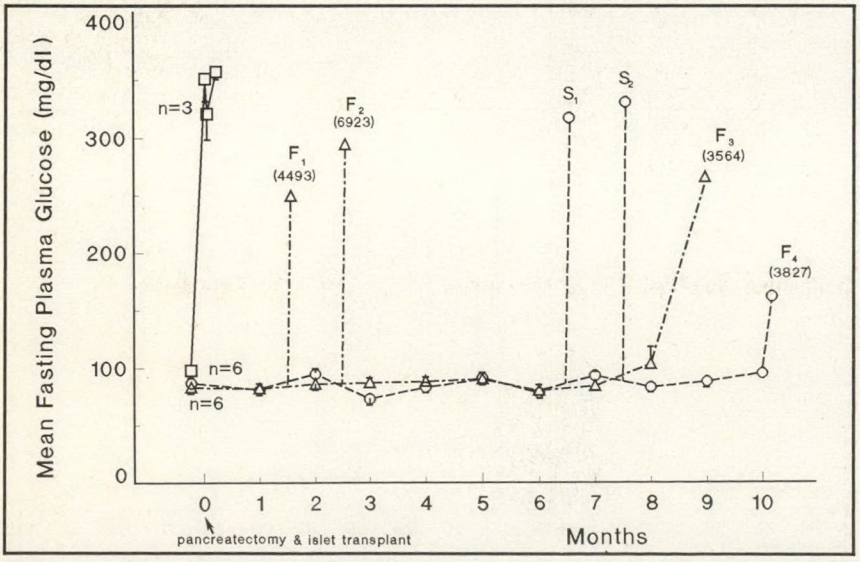


**FIG. 1 — Fasting plasma glucose levels (mg/dl) after autoimplantation of purified islets in liver (triangles) or spleen (circles). Normoglycemia was maintained for more than 1 month in all dogs and hyperglycemic response to splenectomy (S) proves graft function. Delayed failures (F) of graft function were observed in three liver recipients after 6 weeks, 2 months and 8 months. One splenic graft failed at 10 months. Squares = Apancreatic control dogs. Numbers in brackets indicate no. of islets/kg.**

### *Allografts*

Doses of 8645 ± 1149 islets/kg were refluxed into the spleens of seven dogs. In one recipient with initial CsA levels less than 300 μg/L the graft failed at 9 days. Figure 3 shows the results for six dogs that had initial CsA levels of more than 300 μg/L. Compared with apancreatic dogs, the allograft recipients showed immediate fasting normoglycemia, which was maintained for more than 30 days. The fasting plasma glucose value was always higher with allografts than autografts ($p < 0.05$).

## Discussion

Large mammals are the most suitable models for studying the clinical application of islet cell transplantation. The compact pancreas in these species requires three key steps in islet separation: adequate intralobular disruption of the connective tissue stroma, avoidance of mechanical trauma to the islets and density gradient purification.[6–8] We have used these principles to isolate an average of 123 000 highly purified islets. Function was assessed by prolonged follow-up after autoimplantation or alloimplantation.

The purity of the preparations and the small graft mass (0.75 g) allowed us to embolize the tissue to

the liver. Although a transient rise in portal pressure occurred, portal hypertension was not a problem, in contrast with previous studies[4] in which impure preparations were used. At the outset, fasting plasma glucose levels were normal in all autograft recipients and there was no significant difference between the two groups. On prolonged follow-up, delayed autograft failures occurred, as previously observed for intraportal canine islet grafts.[5] Although similar quantities of islets were implanted into the liver and spleen, in our study three of the four failures were in recipients of liver implants. This may have been due to fatigue of an initial marginally adequate mass of islets, but this does not account for the observation that two of the intraportal failures occurred after greater than average numbers of islets were implanted. Alternative mechanisms for delayed failure may be reduced engraftment in the intraportal location or chronic stimulation of the islets by hyperglycemia within the portal venous blood. Because of the small number of grafts in each of the two groups, statistical analysis cannot be used to validate the observation that they failed more frequently when implanted into the liver.

Serial glucose tolerance tests showed that the K value had declined significantly ($p < 0.05$) from pretransplant levels in both autograft groups, but levels in each were similar and the dogs remained nondiabetic (K > 1.0%/min). The reduced level postoperatively was likely due to a smaller mass of functioning B cells, as reflected by the lower plasma insulin response after glucose challenge. A qualitative difference in insulin release was seen between the group 2 dogs, showing a peak response within 1 minute, and group 1 dogs whose peak response was delayed to 5 to 10 minutes. This may result from reduced hepatic extraction of insulin, which is released directly from intrahepatic islets into the postsinusoidal hepatic veins.

Allografts of purified islets induced fasting normoglycemia, evident throughout the 30-day follow-up, when initial CsA trough blood levels were more than 300 $\mu g/L$. When one dog had initial levels

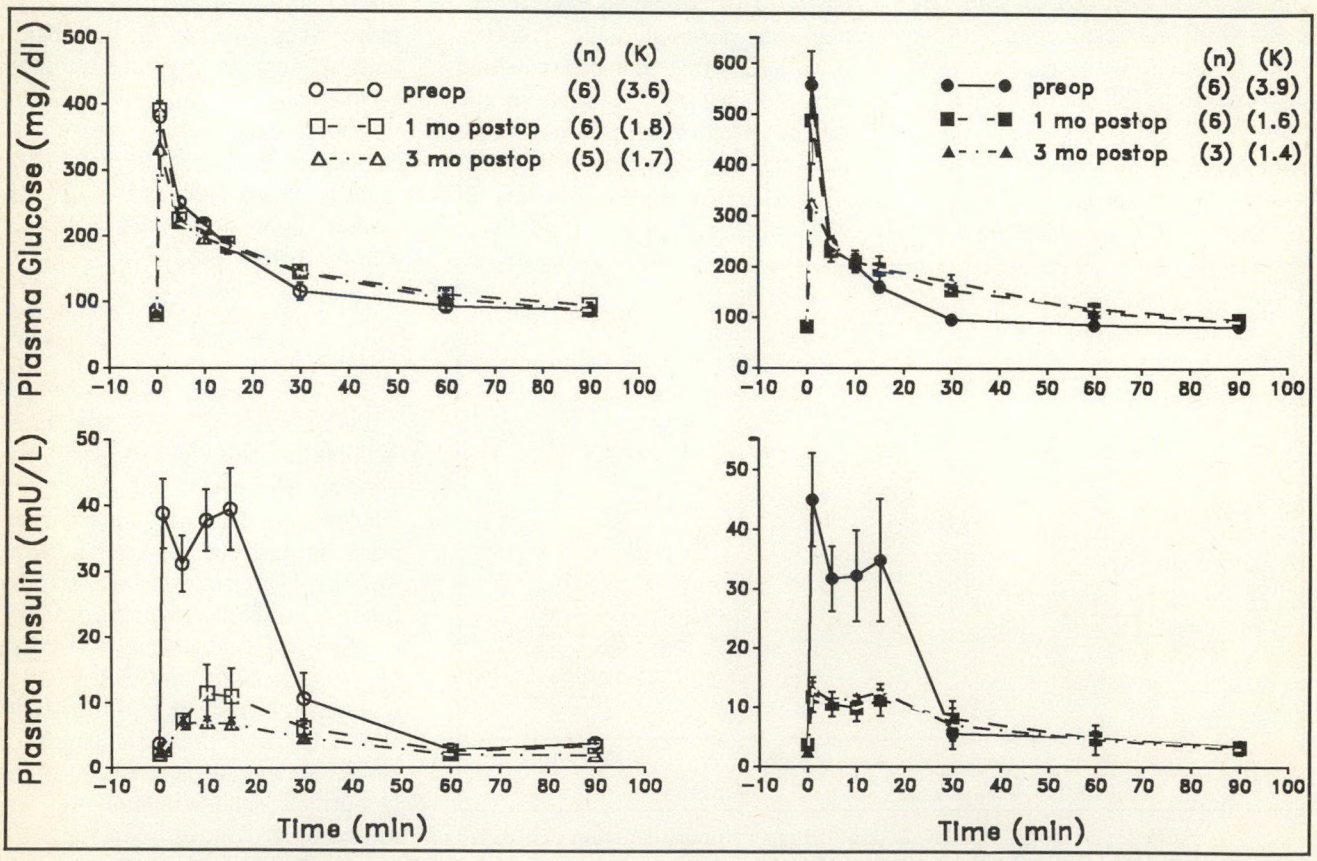


Fig. 2a Fig. 2b

FIG. 2 — Response to intravenous glucose (0.5 g/kg) after (a) splenic or (b) liver autoimplantation showing plasma glucose (mg/dl) and corresponding plasma insulin (mU/L) levels. Rate of glucose decline is slower postoperatively and is accompanied by reduced insulin response. Peak insulin response occurred at 5 to 10 minutes in spleen recipients (a) and at 1 minute in liver recipients (b). n = number of dogs, K = decline of glucose level (%/min).

below 300 μg/L, rejection occurred at 9 days, a finding similar to that of the nonimmunosuppressed controls. Greater numbers of islets were available for allografts than autografts and provided a mass of endocrine tissue well in excess of the critical amount that we found necessary to induce normoglycemia. We believe this enabled us to distinguish graft failure due to rejection rather than fatigue of a marginally adequate islet mass, inadequate engraftment or the toxic effects of CsA. Furthermore, islets were not allografted into the liver because of the frequency of delayed autograft failures at this site. The results showed that function of allografts of pure islets was assured when an adequate mass of tissue from one donor was implanted into a CsA-immunosuppressed recipient. This compares favourably with the results of Alejandro and associates[12] who frequently required purified islets from multiple donor dogs to provide adequate graft function in one recipient and Kneteman and colleagues[13] who used impure pancreatic microfragments. The high levels of CsA required to prevent allograft rejection may, at least in part, have accounted for the higher plasma glucose levels seen in the allograft recipients, but did not cause graft failure within 30 days.

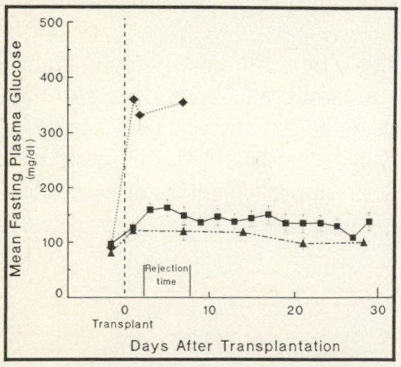


**FIG. 3 — Results of alloimplantation of pure islets into spleen with CsA immunosuppression (squares). Compared with three apancreatic controls (diamonds) normoglycemia occurred immediately and was maintained throughout study in six recipients of CsA at trough serum levels greater than 300 μg/L. Fasting plasma glucose (mg/dl) after splenic allograft implantation was higher than that after splenic autograft implantation (triangles).**

A critical question is, Do the results of our experiments in a large mammal suggest that islet transplantation can be made to work in man? Three key observations may assist us in achieving this difficult goal. First, earlier attempts at human islet transplantation did not account for an accurately quantified mass of viable islets. Our data indicate that more than 5000 islets with an average size of 120 μm must be provided per kilogram of body weight to induce long-term normoglycemia consistently in dogs.[9] Since human islets are larger (150 μm), a 70-kg adult recipient would require 2895 islets/kg or approximately 202 640 islets. We recently used the described isolation procedure to isolate pure viable human islets and found that yields of this order can be achieved.[14] Second, delayed failures of autograft function can occur and the factors responsible for this require further study. Our data suggest that the intraportal site, if chosen for implantation, may play a role. Third, when allografts are implanted, the adverse effects of immunosuppressive agents on islet function are of concern. Among these are the effects of steroids and azathioprine[13] and potential adverse effects of CsA.[15] Our data suggest that function of pure islets can be assured when CsA alone is used; however, the high serum trough levels of CsA would cause serious toxicity in humans. Therefore, some form of islet allograft immunomodulation may be needed to reduce the requirements for immunosuppression.

In summary, our data show that purified islets of Langerhans can maintain prolonged fasting normoglycemia in a large mammal. Some delayed failures of autograft function occur, which may be due to the intraportal site of implantation. Single-donor purified islets induced normoglycemia after alloimplantation into pancreatectomized recipients on CsA immunosuppression who had adequate serum CsA levels. This information will promote studies on immunomodulation of islet allografts in large mammals and encourage a realistic approach to clinical islet transplantation for juvenile onset diabetes.

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# SESAP V Critique

**Items 253–255**

Diagnostic techniques used in patients with soft tissue sarcomas define the location, nature, and extent of the disease. Conventional roentgenograms may demonstrate deformity of fascial planes and tumor calcification. Angiography can diagnose tumor vascularity, extent of disease, and relationship to major vessels, and may be used for infusion chemotherapy and tumor embolization. Ultrasonography differentiates cystic, solid, and complex masses. Computed tomography, the most useful radiographic procedure for axial soft tissue sarcomas, allows recognition of alterations in compartment anatomy. Because fewer than 5% of patients with soft tissue sarcoma have regional node involvement, lymphangiography is infrequently of value.

Although small superficial soft tissue tumors are suitable for excisional biopsy, incisional biopsy is preferred for adequate sampling of large lesions. The biopsy site must be included in the definitive surgical resection. Needle aspiration and "core" biopsies may be acceptable for metastatic disease, but for most tumors, the tissue obtained may be insufficient for a full pathologic evaluation. Wide local excision should not be performed until a tissue diagnosis has been established.

Wide anatomic, soft-part resection is indicated for liposarcoma of an extremity. The resection should include previous biopsy sites and a wide margin of uninvolved tissue. The role of additional treatment in the management of patients with soft tissue sarcomas is not currently well-defined. Radiation therapy may be used preoperatively to reduce the size and deep fixation of a tumor, and postoperatively to eradicate possible residual disease. Preliminary results with adjuvant postoperative chemotherapy suggest an improvement in disease-free and over-all survival. Although preoperative regional infusion chemotherapy has been used, no evidence currently favors preoperative systemic chemotherapy.

253 [E] 254 [B] 255 [E]

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# Oophorovesicular–Colonic Fistula: a Rare Complication of Crohn's Disease

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**Salpingitis and vesicular fistulas are rare complications of Crohn's disease. In this report the authors describe a case of oophorovesicular–colonic fistula secondary to Crohn's disease. The patient presented with bleeding from the bladder during menstruation, fecaluria and pneumaturia. A single-stage left salpingo-oophorectomy, sigmoid resection and repair of the fistula were carried out, with complete resolution of symptoms and preservation of fertility potential.**

**Les salpingites et les fistules vésiculaires sont deux complications rares de la maladie de Cröhn. On décrit dans cet article un cas de fistule ovario-vésciulo–colique secondaire à une maladie de Cröhn. La patiente montrait des signes de saignement par voie vesicale durant les menstruations, de fécalurie et de pneumaturie. Une intervention en un temps, comprenant une salpingo-ovariectomie gauche, une résection sigmoïdienne et une réparation de la fistule, amena une résolution complète des symptômes, avec conservation possible de la fertilité.**

Crohn's disease is often complicated by fistula formation but salpingitis and vesicular fistulas are both rare. We report a case in which the patient had an oophorovesicular–colonic fistula secondary to Crohn's disease.

## Case Report

A 31-year-old woman presented with complaints of crampy lower abdominal pain, generalized malaise, weight loss and bloody diarrhea, diagnosed by barium enema examination and colonoscopy as Crohn's disease. Her symptoms resolved with steroid treatment. She returned 16 months later with diffuse lower abdominal pain and a left lower quadrant mass which was found at laparoscopy to involve the left adnexa, sigmoid colon and uterus. The patient was treated with broad-spectrum antibiotics. There was some shrinkage of the mass, but 3 weeks later she complained of hematuria, which subsequently became cyclic and was accompanied by urinary frequency, urgency, pneumaturia and fecaluria.

Culture of a urine sample grew *Proteus mirabilis*, *Escherichia coli* and *Staphylococcus* sp, all with more than 100 000 colonies/ml of urine.

An intravenous pyelogram revealed a dilated left ureter with mild hydronephrosis. A Hypaque enema examination demonstrated a fistulous connection between bowel and bladder, and contrast computed to-

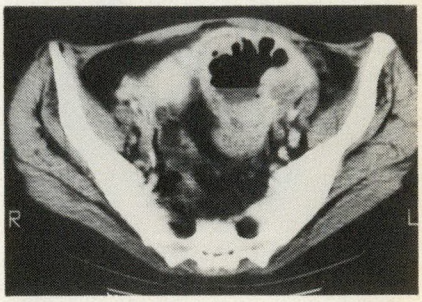

**FIG. 1 — Computed tomogram demonstrating gas-containing left adnexal mass.**

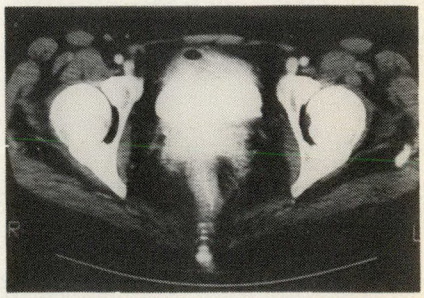

**FIG. 2 — Computed tomogram of pelvis revealing air in bladder with intravenous contrast.**

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mography of the abdomen (Fig. 1) and pelvis (Fig. 2) confirmed dilatation of the left ureter and showed evidence of a poorly defined soft-tissue mass involving uterus, bladder and colon. Contrast medium was evident in the uterus and left fallopian tube.

Cystoscopy revealed bullous edema of the bladder wall and a small fistulous opening 1.5 cm posterior to the ureteral orifices. Diffuse mucosal inflammation with pseudopolyps at 25 to 30 cm was seen on flexible sigmoidoscopy and granulation tissue was seen protruding from the cervical os on vaginal examination.

We performed a single-stage left oophorectomy, salpingectomy, anterior sigmoid resection (with end-to-end anastomosis) and closed the vesicular fistula tract. The right fallopian tube and uterus appeared unaffected and, to preserve fertility, were not removed. The operative specimen (Fig. 3) revealed active inflammatory changes in the sigmoid colon consistent with Crohn's disease. At follow-up 3 months later the patient was asymptomatic and having normal menstrual periods.

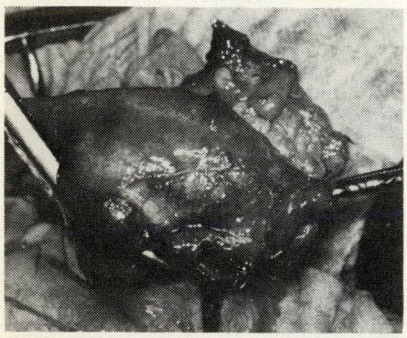

**FIG. 3 — Left adnexal mass connecting left tube, ovary, bladder and colon.**

## Discussion

Crohn's disease is commonly complicated by the formation of fistulas between the involved bowel and adjacent organs. Genitourinary complications are reported in 4% to 10% of patients.[1] However, both salpingitis and enterovesical fistulas are extremely rare manifestations of active Crohn's disease.[2] Isolated fistulas have been reported involving a fallopian tube, uterus, vagina and urethra.[1] Crohn and Yarnis[3] described two cases of fistula formation between the ileum and right fallopian tube, and Wlodarski and Trainer[2] reported isolated cases of Crohn's disease associated with right oophoritis.

Patients who have bowel–bladder fistulas present with urinary frequency, urgency, dysuria, pneumaturia and fecaluria.[4–7] In our case fistulous connection with the left ovary was unusual and ovulation into the tract provided the additional symptom complex of cyclic hematuria.

The combined urologic and radiologic investigations permitted accurate preoperative diagnosis of the condition and successful multiteam surgery with preservation of fertility potential.

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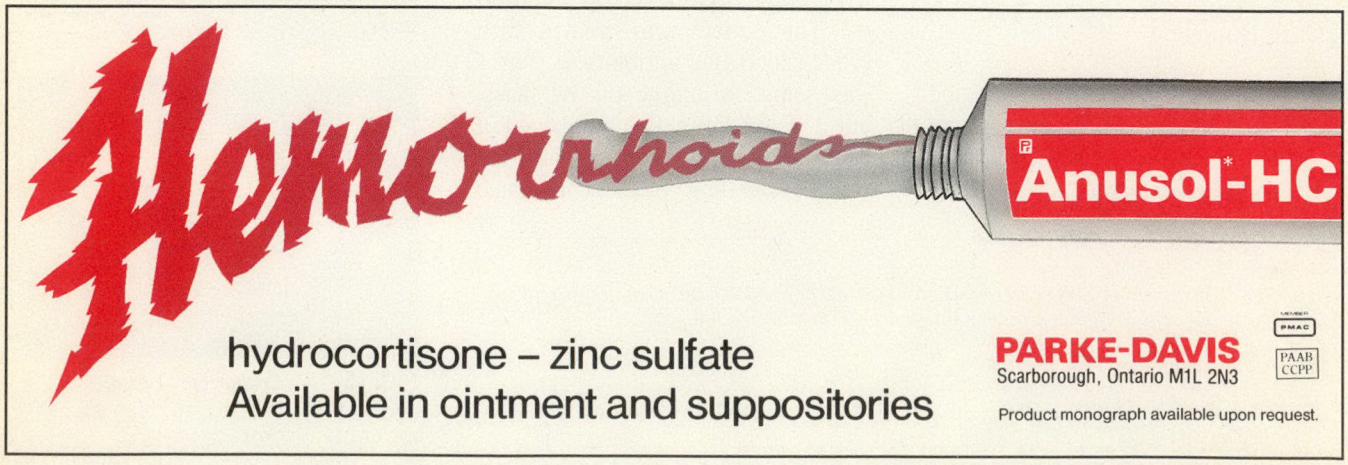

# Fine-Needle Aspiration Biopsy of an Islet Cell Tumour Simulating Pancreatic Carcinoma

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**The importance of distinguishing between malignant islet cell tumour and pancreatic carcinoma is emphasized in this report of a 57-year-old woman who presented with an epigastric mass. Clinically and radiologically it was diagnosed as a pancreatic adenocarcinoma. A fine-needle aspiration biopsy specimen obtained under ultrasonic guidance showed tumour cells suggestive of an islet cell tumour. Immunostaining and electron microscopy were performed on the aspirate. The tumour cells stained positive with antibodies to keratin, glucagon and gastrin; ultrastructural examination revealed neurosecretory granules, confirming the diagnosis of an islet cell tumour. Angiography was performed to assess the possibility of debulking the mass. This case demonstrates the value of immunohistochemistry and electron microscopy on fine-needle aspiration biopsy specimens of the pancreas to differentiate islet cell tumours, which are potentially curable, from pancreatic adenocarcinomas, which carry a 5-year survival rate of less than 2%.**

**On souligne dans cet article l'importance de savoir distinguer une tumeur maligne des cellules insulaires d'un carcinome pancréatique. Le cas d'une femme de 57 ans présentant une masse épigastrique sert à illustrer le fait. Le tableau clinique et radiologique était compatible avec un diagnostic d'adénocarcinome pancréatique. Une ponction-biopsie à l'aiguille fine obtenue sous échographie révéla des cellules tumorales évocatrices d'un insulinome. L'échantillon de biopsie fut soumis à une immuno-coloration et à la microscopie électronique. Les cellules tumorales présentèrent une coloration positive avec des anticorps contre la kératine, le glucagon et la gastrine; l'examen ultrastructural révéla des granules neurosécrétoires confirmant le diagnostic d'un insulinome. Une angiographie fut pratiquée afin d'évaluer la possibilité de réduire la masse tumorale. L'étude immunohistochimique et l'examen au microscope électronique des échantillons de ponction-biopsie sont utiles pour différencier les insulinomes qui sont curables, des adénocarcinomes pancréatiques, lesquels présentent une survie à 5 ans de moins de 2%.**

Pancreatic carcinoma has a poor prognosis, the 5-year survival rate being less than 2%.[1] In spite of modern imaging techniques only 15% to 20% of tumours diagnosed are potentially resectable. Occasionally, pancreatic masses with more favourable prognoses, such as islet cell tumours, may mimic adenocarcinomas, and in such cases multidisciplinary investigations — radiology, fine-needle aspiration cytology with immunopathology and electron microscopy — can give a definitive diagnosis without resort to more invasive techniques. We present a case of non-functioning islet cell tumour in which the patient had clinical manifestations of a pancreatic adenocarcinoma. Our experience demonstrates the feasibility of using special techniques on material obtained by fine-needle aspiration to reach a conclusive diagnosis.

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## Case Report

A 57-year-old woman had a 1-month history of increasing epigastric pain radiating to the right side and back. During this time she lost 6.4 kg and became constipated. A hard, fixed epigastric mass, 10 cm in diameter, was palpable. Ultrasonography and computed tomography (Figs. 1 and 2) suggested a pancreatic neoplasm. The computed tomogram showed superior mesenteric arterial and venous encasement, indicating that the mass was unresectable (Fig. 2). At endoscopic retrograde cholangiopancreatography (ERCP) only the common bile duct could be cannulated, and the ampullary segment was narrowed. Fine-needle aspiration was carried out under ultrasonic guidance. The resulting diagnosis of islet cell tu-

mour led to angiography, which showed a mass involving the pancreatic head, neck and uncinate process, encasing the superior mesenteric vein (Fig. 3). Laparotomy was performed with the intention of debulking the tumour, but this was impossible because of its vascularity. The patient was subsequently discharged from hospital and chemotherapy was started. Periodic sonograms showed gradual enlargement of the tumour and dilatation of the common bile duct. Hepatic metastases developed and the patient died 1 year after her initial presentation.

## Diagnosis

*Methods*

A portion of the specimen obtained by fine-needle aspiration was alcohol-fixed and stained by the Papanicolaou method. Small fragments were also fixed in Bouin's fixative for a cell block preparation. The biopsy tissue obtained from surgery was fixed in 10% buffered formalin. For light microscopy, sections were stained with hematoxylin and eosin.

The Bouin-fixed material and the formalin-fixed paraffin-embedded tissue sections were stained by the peroxidase antiperoxidase technique using antibodies to insulin, glucagon, serotonin, gastrin and low-molecular-weight keratin, which recognizes keratins of 39, 43 and 50 kilodaltons. The antibodies were obtained from Dako Corp., Santa Barbara, Calif., Immuno-Nuclear Corp., Stillwater, Minn. and Beckton Dickinson, Mountain View, Calif. Appropriate negative and positive controls were used.

A portion of the needle aspirate from the pancreas was placed in universal fixative. The specimen was centrifuged and the pellet processed for routine electron microscopy. The sections were stained with uranyl acetate and lead citrate and examined by a Phillips 300 electron microscope.

*Results*

The fine-needle aspirate from the pancreas showed clusters of uniform cells with little pleomorphism (Fig. 4) and an occasional mitotic figure — features suggestive of an islet cell tumour. Light microscopy of the subsequent surgical specimen confirmed the diagnosis of an islet cell tumour.

Immunohistochemical staining of the cell block of the needle aspirate and the biopsy specimen showed positive staining of the tumour cells for glucagon (Fig. 5a), serotonin and gastrin but not for insulin (Fig. 5b). They also stained positively for low-molecular-weight keratin.

Ultrastructural examination of the aspirate revealed nests of tumour cells joined by desmosomes and containing numerous neurosecretory granules (Fig. 6), thus confirming the diagnosis of islet cell tumour. The granules varied in size from 130 to 230 nm, compatible in size and morphology with glycogen and gastrin granules. No insulin granules could be seen.

## Discussion

It is important for therapy and prognosis to distinguish islet cell tumours from pancreatic adenocarcinomas. Prolonged survival has been reported after excision of the former, even those larger than 10 cm,[2] and isolated involvement of the portal vein does not preclude resection.[2] Adjuvant chemotherapy may provide effective palliation in one-third of patients with malignant islet cell tumours.[2,3] Fine-needle aspiration biopsy is an effective method of obtaining material for diagnosing pancreatic carcinoma.[4-6] The risks are minimal, the accuracy is about 86% and the technique obviates laparotomy.[4] Islet cell tumours may be diagnosed from the cytology material but are sometimes difficult to differentiate from pancreatic carcinoma.

Radiology plays an important role in the diagnosis and manage-

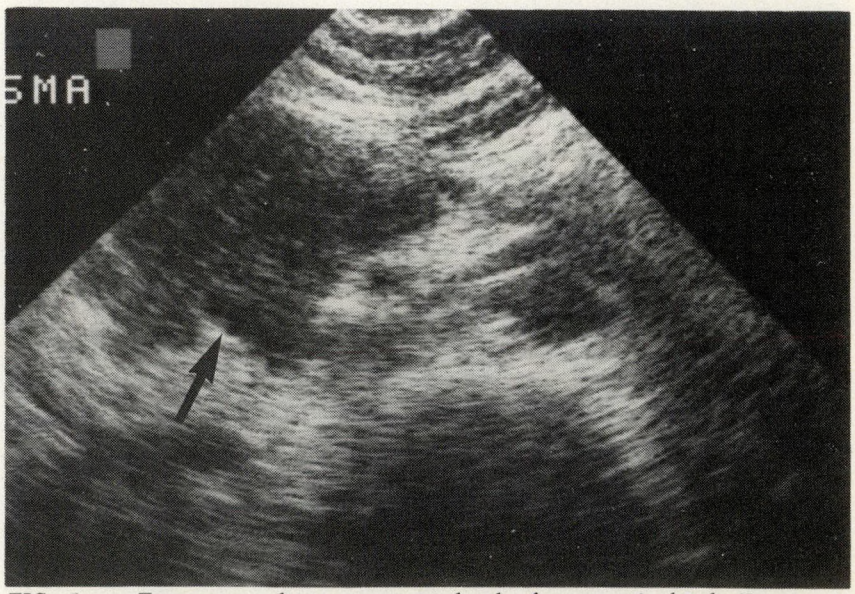


**FIG. 1 — Transverse ultasonogram at level of pancreatic head. Tumour is hypoechoic and encases superior mesenteric vein (arrow).**

ment of pancreatic lesions.[7-9] Functioning islet cell tumours usually present while still small. They are diagnosed biochemically, and radiologic techniques are used for preoperative localization.[3,10] Nonfunctioning islet cell tumours resemble adenocarcinomas in that they are usually large at the time of presentation and may be assessed as "malignant" and unresectable. Clinically, both types of tumour can present such symptoms as abdominal pain, nausea, vomiting, malaise, weight loss and jaundice. Although radiology is helpful in their evaluation,[3] they can both have the same radiologic appearance. They are seen as irregular, solid masses encasing the adjacent vessels on ultrasonography and computed tomography.[10,11] They produce abrupt, irregular strictures or occlusions of the pancreatic and common bile ducts on ERCP; they also are seen displacing and invading the stomach and duodenum on barium contrast studies.[11] Computed tomography may suggest an islet cell tumour if contrast enhancement shows a homogeneous vascular or hypervascular lesion.[10,12] In our patient the diagnosis was not suspected on computed tomography because the tumour had multiple areas of hemorrhage and necrosis resulting in a heterogeneous appearance. Adenocarcinoma and "malignant" islet cell tumours can be differentiated by selective arteriography; both encase and displace the adjacent blood vessels. However, the former are uniformly hypovascular and the latter show vascular or hypervascular areas (capillary blush). Hepatic metastases resemble their respective primary tumours. Arteriography is usually reserved for patients with potentially resectable lesions.[11,13] In our patient, ultrasonography and computed to-

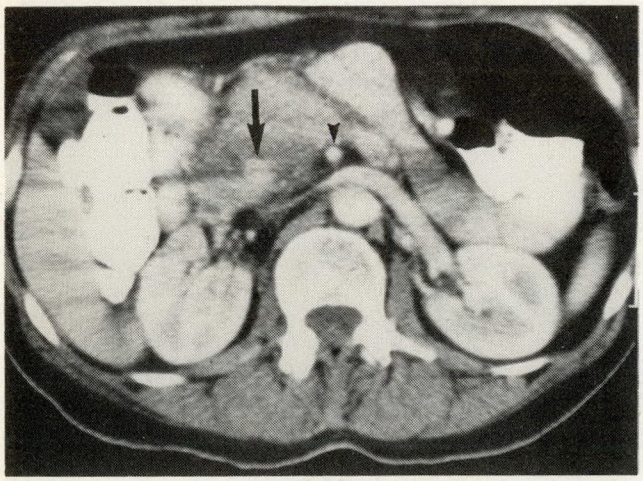

Fig. 2a

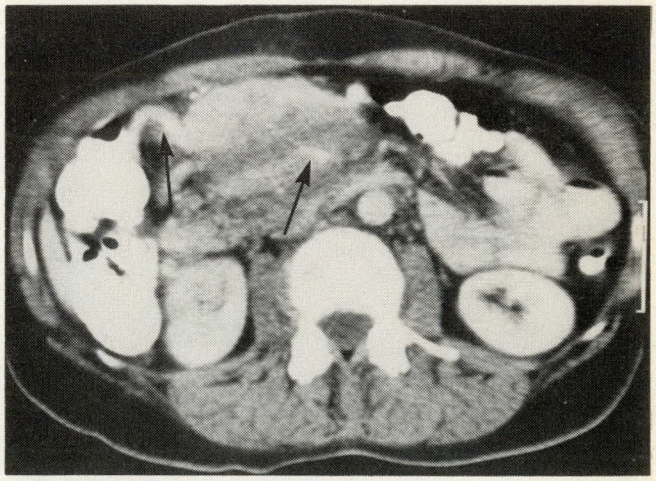

Fig. 2b

FIG. 2 — Computed tomograms at level of pancreatic head. Tumour shows heterogeneous enhancement with intravenous contrast. (a) Superior mesenteric vein (long arrow) and artery (arrowhead) are encased. (b) Dilated right colic veins are seen (arrows).

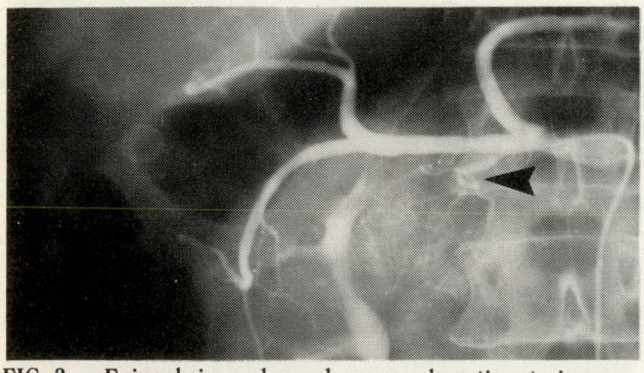

FIG. 3 — Epinephrine-enhanced common hepatic arteriogram. Larger arteries are constricted. Vascular mass is seen in pancreatic head supplied by dorsal pancreatic artery (arrowhead) and branches of gastroduodenal artery.

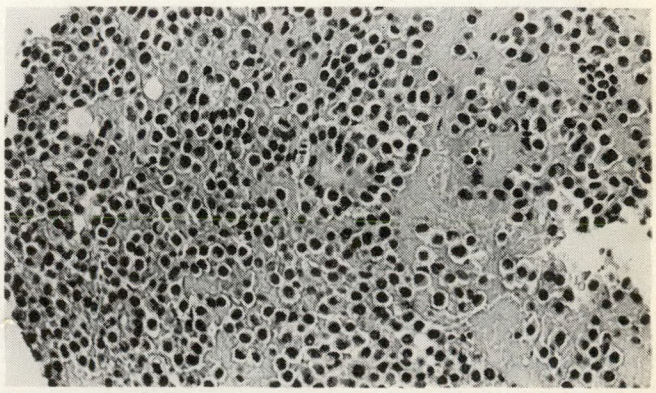

FIG. 4 — Fine-needle aspirate of pancreatic mass shows clusters of uniform cells with little plemorphism (Papanicolaou's stain, original magnification × 240).

mography revealed encasement of the superior mesenteric vessels and therefore unresectability. Arteriography was performed because of the unexpected cytologic diagnosis and the possibility of surgical debulking.

In addition to routine Papanicolaou staining, the cytology material is also suitable for the application of immunohistochemical and ultrastructural techniques.[14-16] The pres-

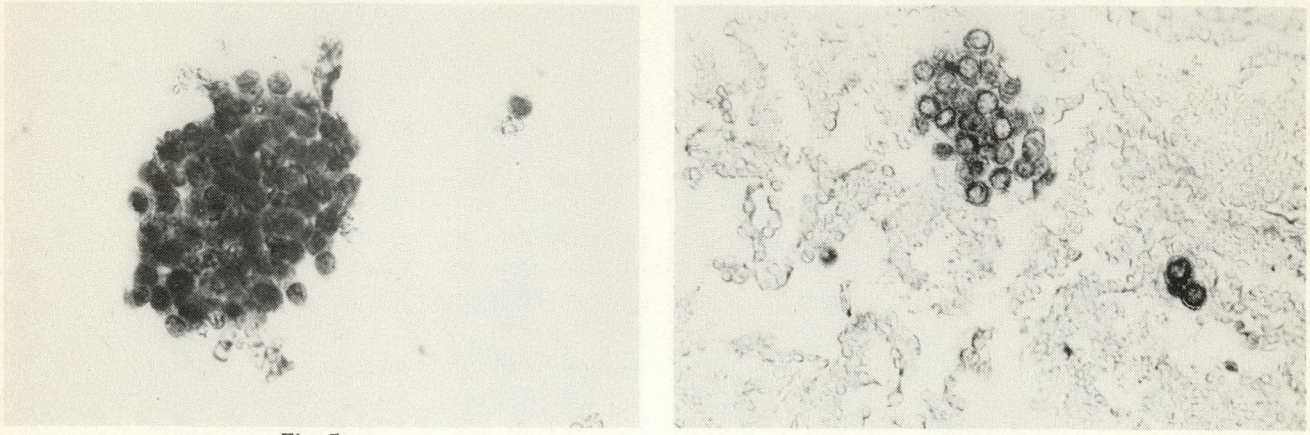

Fig. 5a

Fig. 5b

FIG. 5 — Immunoperoxidase staining of cell block shows (a) positive staining of tumour cells with antibody to glucagon and (b) no staining with antibody to insulin (original magnification × 384).

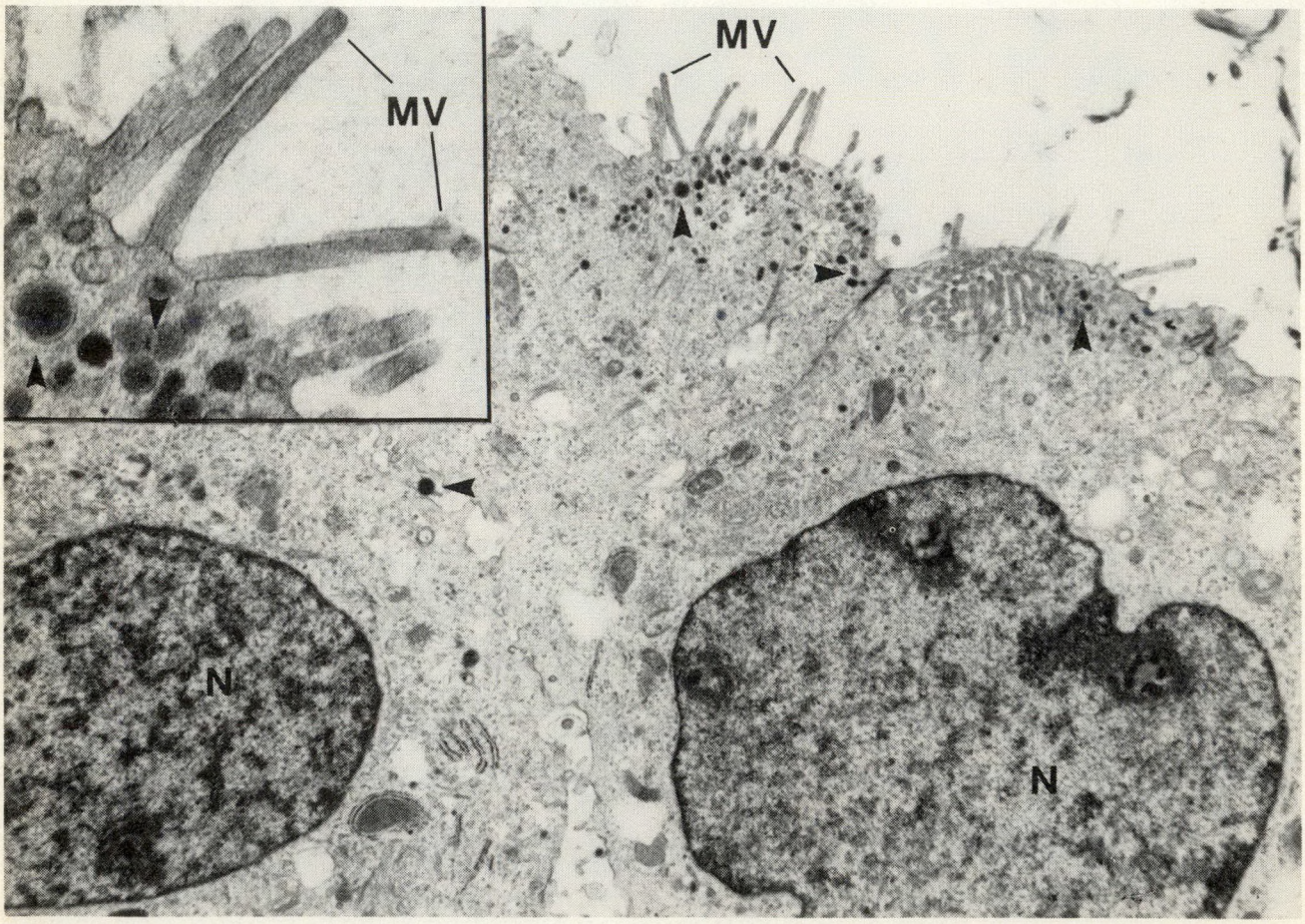


FIG. 6 — Electron photomicrograph of pancreatic aspirate shows cluster of tumour cells joined by desmosomes. Surface is covered by microvilli (MV). Apical portion of cytoplasm contains neurosecretory granules (arrowheads) (original magnification × 9200) which are shown at higher magnification in inset (original magnification × 35 000). N = nucleus.

ence of low-molecular-weight keratins in the tumour cells confirms the epithelial nature of the neoplasm, since keratins are the intermediate filaments that have been detected in both adenocarcinomas and islet cell tumours.[17,18] However, they may not differentiate between these two types of neoplasms. Immunohistochemically, the presence of pancreatic hormones confirms the diagnosis of islet cell tumours.[19] A single hormone or multiple hormones have been detected immunohistochemically in tissue sections of pancreatic endocrine tumours.[19]

No clinical syndrome was evident in our case, indicating that the tumour cells were producing the hormones but not secreting them into the circulation. A block in the secretion of hormones has been described in a number of islet cell tumours.[19] The type of hormone produced may also be of prognostic significance; tumours secreting insulin tend to have a benign course whereas most gastrin-producing tumours are malignant.[20] In this case, the cells were positive for glucagon and gastrin, confirming that the mass was an islet cell tumour. With cells containing gastrin, one would expect the tumour to behave more aggressively than if the cells were producing other hormones. The fact that the tumour was located in the head of the pancreas, was already 10 cm in size at the time of presentation and had not caused biliary obstruction, suggests that it was slow growing and had been present for some time. Thus, the prognosis was considered better than a pancreatic adenocarcinoma but worse than an islet cell tumour producing insulin.

Material obtained from fine-needle aspirates is adequate for ultrastructural evaluation, providing it is representative of the tumour. Even if the tumour is necrotic and the material poorly fixed, neurosecretory granules can still be identified, thus helping to differentiate islet cell tumour from adenocarcinoma.

Fine-needle aspiration is an effective method for diagnosing pancreatic tumours.[5,6] A conclusive diagnosis can be obtained by electron microscopy and immunohistochemistry on the aspirate obtained under ultrasonic guidance. A prognosis may also be made, depending on the hormone produced by the tumour cells, even if it is not secreted into the bloodstream.

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# Residual Hypothermia in Patients Recovering in the Intensive Care Unit From Cardiac Surgery

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**Because of inadequate rewarming or equilibration of body temperature, patients who undergo cardiac surgery with hypothermia often are still hypothermic after arrival in the intensive care unit. The incidence of residual hypothermia and its hemodynamic effects were assessed in this study.**

**Of 82 adults who underwent cardiac surgery, 41 were normothermic with core temperatures of 35.5°C or higher (mean 36.0 ± 0.1°C) and 41 were hypothermic with temperatures below 35.5°C (mean 34.9 ± 0.1°C) on arrival at the intensive care unit ($p < 0.005$). Patients with hypothermia had significantly (1.9 ± 0.1 versus 2.2 ± 0.1, $p < 0.05$) lower cardiac indices. Although not statistically significant, there was a trend toward higher systemic vascular resistance in the patients with hypothermia.**

**The authors conclude that mild residual hypothermia is still common after cardiac surgery and may contribute to the depressed hemodynamic status of these patients.**

**Que ce soit dû à un réchauffement insuffisant ou à un problème d'homéothermie, les patients qui subissent une chirurgie cardiaque sous hypothermie sont souvent encore hypothermiques à leur arrivée aux soins intensifs. La présente étude mesure l'incidence de l'hypothermie résiduelle ainsi que ses effets hémodynamiques.**

**D'un groupe de 82 adultes soumis à une opération cardiaque, 41 étaient normothermiques avec une température de 35.5°C ou plus (moyenne 36.0 ± 0.1°C) à leur arrivée aux soins intensifs, alors que 41 étaient hypothermiques avec une température inférieure à 35.5°C (moyenne 34.9 ± 0.1°C, $p < 0.005$). Les patients souffrant d'hypothermie présentaient un index significativement plus faible (1.9 ± 0.1 par rapport à 2.2 ± 0.1, $p < 0.05$); chez ces mêmes patients on constatait une tendance vers une résistance vasculaire générale plus élevée, quoi que la différence ne soit pas statistiquement significative.**

**Les auteurs concluent qu'il est fréquent de recontrer une faible hypothermie résiduelle après une chirurgie cardiaque. Ceci pourrait contribuer à abaisser le statut hémodynamique de ces patients.**

Systemic hypothermia is widely used during cardiac surgery, and patients are routinely rewarmed before they are taken off cardiopulmonary bypass. Because of inadequate rewarming or equilibration of uneven body temperature, they frequently manifest a drop in body temperature in the early postoperative period.[1,2] Such hypothermia may reduce myocardial contractility and increase myocardial irritability and peripheral resistance, thus adding to afterload in unanesthetized patients. We assessed the incidence of hypothermia after cardiac surgery and determined its possible effects on cardiovascular function.

## Patients and Methods

We reviewed the charts of patients who returned to the intensive care unit after cardiac surgery, for the 3 months from Oct. 1 to Dec. 31, 1986. During this period 82 patients underwent open-heart surgery and were eligible for the study.

They were divided into two groups of 41, according to body core temperature on arrival at the intensive care unit: group 1 was normothermic (core temperature more than 35.5°C as measured with the Swan–Ganz catheter with thermistor tip) and group 2 hypothermic (core temperature less than 35.5°C). Central venous, pulmonary artery and capillary wedge pressures were also measured with the Swan–Ganz catheter. Heart rates and blood pressures were monitored by radial artery cannulation. Cardiac output was determined by the thermodilution method. We used the Gould Cardiac Computer (Critical Care Division, Spectramed Inc., Oxnard, Calif.) to calculate cardiac index, systemic vascular resistance and stroke work index. Student's *t*-test was used to evaluate differences in hemodynamic status between the groups. The $\chi^2$ frequency distribution was used

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to analyse the use of vasodilators and inotropic agents.

## Findings

In group 1 (normothermic) patients the core temperature ranged from 35.5° to 37.7°C and in group 2 (hypothermic) temperature ranged from 34.0° to 35.4°C. Aortocoronary bypass was the most common operation and in both groups males predominated.

The mean cardiopulmonary bypass time and average aortic cross-clamp time were comparable for both groups (Table I).

Comparison of hemodynamic status between the two groups revealed significantly ($p < 0.05$) lower cardiac indices in group 2 (Table II). Although not statistically significant, there was also a trend toward higher systemic vascular resistance in these patients. Stroke work index was not significantly different in the hypothermic patients.

Approximately 25% of the patients in each group initially required inotropic agents after surgery. Similarly, 20% required vasodilator therapy. There was no statistical difference between the two groups in this respect (Table III).

## Discussion

Hypothermia and its physiologic effects have been studied extensively. As the core temperature falls, cell metabolic rate is reduced. This depresses various cell functions and accounts for most of the physiologic changes noted in hypothermia.[3] During cardiac surgery, periods of inadequate systemic circulation may occur, and experiments by Bigelow and colleagues[4] have led to the widespread use of hypothermia in these circumstances. This enables vital tissues to survive periods of anoxia or ischemia.[5]

Early animal studies[6] showed that cardiac output decreases with induced hypothermia. This was also shown[7] to occur in man in the operating-room setting. More recently, Roberts and associates[8] found that 90% of patients who underwent coronary artery bypass grafting displayed a decrease in ejection fraction, left ventricular stroke work index and cardiac index, 2 hours postoperatively. Further studies[9] have shown that after myocardial revascularization there is transient temperature-dependent hemodynamic dysfunction during the rewarming period.

For the purpose of this study we defined hypothermia as a core temperature of less than 35.5°C. Fifty percent of patients were found to be hypothermic on arrival at the intensive care unit after cardiac surgery. Why this happened is uncertain, because all patients are rewarmed after cardiopulmonary bypass, but insufficient rewarming combined with a redistribution of heat to reduce the temperature gradient within body tissues is the likely explanation. Another possible explanation may be the effect of anesthetic drugs on thermoregulation; these agents may impair responses to cooling such as vasoconstriction, shivering and increased metabolism. They also can alter feedback to and from the central nervous system.[10]

Hypothermia decreases myocardial contractility and increases myocardial irritability.[5] Among the parameters of cardiovascular function studied, cardiac index was found to be significantly ($p < 0.05$) lower in patients with hypothermia. This may reflect reduced myocardial contractility. Other findings suggest an increase in peripheral resistance and stroke work index, but the differ-

**Table I** – Clinical Data

| | Group 1 (n = 41) | Group 2 (n = 41) |
|---|---|---|
| Sex (male: female) | 31:10 | 29:12 |
| Mean age (range), yr | 62 (34 – 77) | 62 (32 – 84) |
| Mean bypass time (range), min | 101 (41 – 156) | 96 (43 – 143) |
| Mean aortic cross-clamp time (range), min | 60 (15 – 105) | 57 (14 – 108) |
| Type of surgery, no. of patients | | |
| ACBP | 33 | 35 |
| MVR | 5 | 2 |
| AVR | 1 | 2 |
| MVR/AVR | 1 | 1 |
| AVR/ACBP | 1 | 1 |

ACBP = aortocoronary bypass, MVR = mitral valve replacement, AVR = aortic valve replacement.

**Table II** – Hemodynamic Status (Mean ± SEM) on Arrival at the Intensive Care Unit

| Group | Core temperature, °C | Stroke work index, $g\text{-}m/m^2 \cdot beat^{-1}$ | Cardiac index, $L/min \cdot m^{-2}$ | Systemic vascular resistance, $dyne/s \cdot cm^{-5}$ |
|---|---|---|---|---|
| 1 | 36.0 ± 0.1 (n = 41) | 25.5 ± 1.5 (n = 29) | 2.2 ± 0.1 (n = 36) | 1484 ± 94.6 (n = 34) |
| 2 | 34.9 ± 0.1 (n = 41) | 25.8 ± 2.1 (n = 15) | 1.9 ± 0.1 (n = 27) | 1608.8 ± 98.8 (n = 27) |
| | $p < 0.005$ | NS | $p < 0.05$ | NS |

**Table III** – Use of Pharmacologic Agents

| Group | Inotropic agents, % | Vasodilators, % |
|---|---|---|
| 1 | 26.8 | 22 |
| 2 | 26.8 | 17 |

ences noted were relatively small and were not statistically significant.

Our study revealed that mild residual hypothermia is still common after cardiac surgery. Although generally mild, it may partially account for the hemodynamic dysfunction observed in patients upon their arrival at the intensive care unit. Continued vigilance is needed to prevent residual hypothermia and, thus, cardiac depression during this critical period.

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# Mefoxin* IV/IM

**(sterile cefoxitin sodium, MSD Std.)**

**ANTIBIOTIC**

### ACTION

*In vitro* studies demonstrate that the bactericidal action of cefoxitin, a cephamycin derived from cephamycin C, results from the inhibition of bacterial cell wall synthesis. Evidence suggests that the methoxy group in the 7$\alpha$ position is responsible for the resistance of cefoxitin to degradation by bacterial beta-lactamases.

### INDICATIONS AND CLINICAL USES

#### TREATMENT

The treatment of the following infections when due to susceptible organisms:

1 - Intra-abdominal infections such as peritonitis and intra-abdominal abscess

2 - Gynecological infections such as endometritis and pelvic cellulitis

3 - Septicemia

4 - Urinary tract infections (including those caused by *Serratia marcescens* and *Serratia* spp.)

5 - Lower respiratory tract infections

6 - Bone and joint infections caused by *Staphylococcus aureus*

7 - Soft tissue infections such as cellulitis, abscesses and wound infections

Appropriate culture and susceptibility studies should be performed to determine the susceptibility of the causative organism(s) to MEFOXIN*. Therapy may be started while awaiting the results of these tests, however, modification of the treatment may be required once these results become available.

Organisms particularly appropriate for therapy with MEFOXIN* are:

**Gram positive**
Staphylococci, penicillinase producing and non-producing
Streptococci excluding enterococci

**Gram negative (beta-lactamase producing and non-producing strains)**
*E. coli*
*Klebsiella* species (including *K. pneumoniae*)
*Proteus*, indole positive and negative
*Haemophilus influenzae*
*Providencia* species

**Anaerobes**
*Bacteroides fragilis*

MEFOXIN* may also be appropriate for the treatment of infections involving susceptible strains of both aerobic and anaerobic bacteria.

MEFOXIN* is not active against *Pseudomonas*, most strains of enterococci, many strains of *Enterobacter cloacae*, and methicillin-resistant staphylococci and *Listeria monocytogenes*.

Clinical experience has demonstrated that MEFOXIN* can be administered to patients who are also receiving carbenicillin, gentamicin, tobramycin, or amikacin (see PRECAUTIONS and ADMINISTRATION).

**Intravenous Administration**
The intravenous route is preferable for patients with bacteremia, bacterial septicemia, or other severe or life-threatening infections, or for patients who may be poor risks because of lowered resistance resulting from such debilitating conditions as malnutrition, trauma, surgery, diabetes, heart failure, or malignancy, particularly if shock is present or impending.

#### PROPHYLACTIC USE

MEFOXIN* may be administered perioperatively (preoperatively, intraoperatively and postoperatively) to patients undergoing vaginal or abdominal hysterectomy and abdominal surgery when there is a significant risk of postoperative infection or where the occurrence of postoperative infection is considered to be especially serious.

In patients undergoing cesarean section, intraoperative (after clamping the umbilical cord) and postoperative use of MEFOXIN* may reduce the incidence of surgery related postoperative infections.

Effective prophylactic use depends on the time of administration. MEFOXIN* usually should be given one-half to one hour before the operation. Prophylactic administration should usually be stopped within 12 hours. It has been generally reported that continuing administration of any antibiotic beyond 24 hours following surgery increases the possibility of adverse reactions but, in the majority of surgical procedures, does not reduce the incidence of subsequent infection.

If signs of postsurgical infection should appear, specimens for culture should be obtained for identification of the causative organism(s) so that appropriate therapy may be instituted.

### CONTRAINDICATIONS

MEFOXIN* is contraindicated in persons who have shown hypersensitivity to cefoxitin or to the cephalosporin group of antibiotics.

### WARNINGS

Before therapy with MEFOXIN* is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to MEFOXIN*, cephalosporins, penicillins or other drugs. MEFOXIN* should be given with caution to penicillin-sensitive patients.

There is some clinical and laboratory evidence of partial cross-allergenicity between cephamycins and the other beta-lactam antibiotics, penicillins and cephalosporins. Severe reactions (including anaphylaxis) have been reported with most beta-lactam antibiotics.

Pseudomembranous colitis has been reported with virtually all antibiotics. This colitis can range from mild to life threatening in severity. Antibiotics should therefore be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis. It is important to consider a diagnosis of pseudomembranous colitis in patients who develop diarrhea in association with antibiotic use. While studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis, other causes should also be considered.

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics including MEFOXIN* with caution.

If an allergic reaction to MEFOXIN* occurs, administration of the drug should be discontinued. Serious hypersensitivity reactions may require treatment with epinephrine and other emergency measures.

### PRECAUTIONS

The total daily dosage should be reduced when MEFOXIN* is administered to patients with transient or persistent reduction of urinary output due to renal insufficiency (see DOSAGE AND ADMINISTRATION) because high and prolonged serum antibiotic concentrations can occur from usual doses.

In patients treated with MEFOXIN* a false-positive reaction to glucose in the urine may occur with Benedict's or Fehling's solutions but not with the use of specific glucose oxidase methods.

Using the Jaffe Method, falsely high creatinine values in serum may occur if serum concentrations of cefoxitin exceed 100 $\mu$g/mL. Serum samples from patients treated with MEFOXIN* should not be analyzed for creatinine if withdrawn within two hours of drug administration.

Increased nephrotoxicity has been reported following concomitant administration of cephalosporins and aminoglycoside antibiotics.

The safety of MEFOXIN* in the treatment of infections during pregnancy has not been established. If the administration of

MEFOXIN* to pregnant patients is considered necessary, its use requires that the anticipated benefits be weighed against possible hazards to the fetus. Reproductive and teratogenic studies have been performed in mice and rats and have revealed no evidence of impaired fertility or harm to the fetus due to MEFOXIN*.

Cefoxitin has been observed in the milk of nursing mothers receiving the drug.

Prolonged use of MEFOXIN* may result in the overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential and if superinfection occurs during therapy, appropriate measures should be taken. Should an organism become resistant during antibiotic therapy, another antibiotic should be substituted.

In children 3 months of age or older, higher doses of MEFOXIN* (100 mg/kg/day and above) have been associated with an increased incidence of eosinophilia and elevated SGOT.

## ADVERSE REACTIONS

MEFOXIN* is generally well tolerated. Adverse reactions rarely required cessation of treatment and usually have been mild and transient.

**Local Reactions**
Thrombophlebitis has occurred with intravenous administration. Some degree of pain and tenderness is usually experienced after intramuscular injections using water. Induration has occasionally been reported.

**Allergic**
Maculopapular rash, urticaria, pruritus, eosinophilia, fever and other allergic reactions have been noted.

**Gastrointestinal**
Symptoms of pseudomembranous colitis can appear during or after antibiotic treatment. Nausea and vomiting have been reported rarely.

**Blood**
Transient eosinophilia, leukopenia, neutropenia, hemolytic anemia, and thrombocytopenia have been reported. Some individuals, particularly those with azotemia, may develop positive direct Coombs tests during therapy with MEFOXIN*.

**Liver Function**
Transient elevations in SGOT, SGPT, serum LDH, and serum alkaline phosphatase have been reported.

**Kidney**
Elevations in serum creatinine and/or blood urea nitrogen levels have been observed. As with the cephalosporins, acute renal failure has been reported rarely. The role of MEFOXIN* in changes in renal function tests is difficult to assess, since factors predisposing to prerenal azotemia or to impaired renal function have often been present.

## TREATMENT OF OVERDOSE

Other than general supportive treatment, no specific antidote is known. MEFOXIN* can be eliminated by dialysis in patients with renal insufficiency.

## DOSAGE AND ADMINISTRATION

MEFOXIN* may be administered intravenously or intramuscularly when required. (See complete monograph on ADMINISTRATION and RECONSTITUTION.)

### TREATMENT DOSAGE

**Adults**

The usual adult dosage is 1 g or 2 g of MEFOXIN* every 6 to 8 hours. Dosage and route of administration should be determined by severity of infection, susceptibility of the causative organisms, and condition of the patient. The usual adult dosages are shown in the Table below.

**Usual Adult Dosage**

| Type of infection | Daily Dosage | Frequency and Route |
|---|---|---|
| Uncomplicated forms* of infections such as pneumonia, urinary tract infection, soft tissue infection | 3-4 g | 1 g every 6-8 h I.V. or I.M. |
| Moderately severe or severe infections | 6-8 g | 1 g every 4 h or 2 g every 6-8 h I.V. |
| Infections commonly needing antibiotics in higher dosage (e.g. gas gangrene) | 12 g | 2 g every 4 h or 3 g every 6 h I.V. |

*Including patients in whom bacteremia is absent or unlikely

Therapy may be started while awaiting the results of susceptibility testing.

Antibiotic therapy for group A beta-hemolytic streptococcal infections should be maintained for at least 10 days to guard against the risk of rheumatic fever or glomerulonephritis. In staphylococcal and other infections involving a collection of pus, surgical drainage should be carried out where indicated.

**Adults with Impaired Renal Function**

MEFOXIN* may be used in patients with reduced renal function but a reduced dosage should be employed and it is advisable to monitor serum levels in patients with severe impairment.

In adults with renal insufficiency, an initial loading dose of 1 g to 2 g should be given. After a loading dose, the following recommendations for **maintenance dosage** may be used as a guide:

| RENAL FUNCTION | CREATININE CLEARANCE mL/min | DOSE | FREQUENCY |
|---|---|---|---|
| Mild impairment | 50-30 | 1-2 g | every 8-12 h |
| Moderate impairment | 29-10 | 1-2 g | every 12-24 h |
| Severe impairment | 9-5 | 0.5-1 g | every 12-24 h |
| Essentially no function | <5 | 0.5-1 g | every 24-48 h |

In the patient undergoing hemodialysis, the loading dose of 1-2 g should be given after each hemodialysis, and the maintenance dose should be given as indicated in the Table above.

**Neonates (Including Premature Infants), Infants and Children** (See WARNINGS for Neonates under ADMINISTRATION in the complete monograph.)

| | |
|---|---|
| **Premature Infants with Body Weights Above 1500 g** | 20-40 mg/kg every 12 h I.V. |
| **Neonates** | |
| 0-1 week of age | 20-40 mg/kg every 12 h I.V. |
| 1-4 weeks of age | 20-40 mg/kg every 8 h I.V. |
| **Infants** | |
| 1 month to 2 years of age | 20-40 mg/kg every 6 h or every 8 h I.M. or I.V. |
| **Children** | 20-40 mg/kg every 6 h or every 8 h I.M. or I.V. |

In severe infections, the total daily dosage in infants and children may be increased to 200 mg/kg, but not to exceed 12 g per day.

MEFOXIN* is not recommended for the therapy of meningitis. If meningitis is suspected, an appropriate antibiotic should be used.

At present there is insufficient data to recommend a specific dosage for children with impaired renal function. However, if the administration of MEFOXIN* is deemed to be essential the dosage should be modified consistent with the recommendations for adults (see Table above).

### PROPHYLACTIC USE

For prophylactic use, a three-dose regimen of MEFOXIN* is recommended as follows:

**Vaginal or abdominal hysterectomy and abdominal surgery**

2 g administered intramuscularly or intravenously just prior to surgery (approximately one-half to one hour before initial incision).

The second and third 2 g doses should be administered at 2-6 hour intervals after the initial dose.

**Cesarean Section**

The first dose of 2 g should be administered intravenously as soon as the umbilical cord has been clamped. The second and third 2 g doses should be given intravenously or intramuscularly four hours and eight hours after the first dose.

## AVAILABILITY

MEFOXIN* is supplied as sterile powder in boxes of 10 vials:

3356 Ca - 1 g cefoxitin as sodium salt
3357 Ca - 2 g cefoxitin as sodium salt

**Storage**
MEFOXIN* in the dry state should be stored below 30°C.

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# Complications immédiates de la résection transurétrale de la prostate: étude de 1000 cas consécutifs

Jean-Marie Paquin, MD, FRCSC; Jean-Paul Perreault, MD, FRCSC; Raymond Faucher, MD, FRCSC; François Mauffette, MD, FRCSC; Luc Valiquette, MD, FRCSC; Steven Lapointe, MD, FRCSC

**Les auteurs ont révisé les dossiers de 1000 patients qui ont subi une résection transurétrale de la prostate. L'étude a porté sur les 30 jours postopératoires. Des complications ont été rencontrées chez 139 patients et il y eut 6 décès. Les problèmes d'infection (urinaire dans 63 cas et septicémie dans 23 cas) sont les plus fréquents, suivis de l'hémorragie et de la rétention. Les décès étaient reliés à des causes cardiaques.**

**The authors reviewed the charts of 1000 patients who underwent transurethral resection of the prostate. When the 30-day postoperative period was studied, it was found that 139 patients suffered complications and 6 died. Infectious complications (urinary tract in 63 cases and septicemia in 23 cases) were the commonest followed by hemorrhage and urinary retention. The deaths were related to cardiac problems.**

La résection transurétrale de la prostate est une intervention pratiquée de façon quotidienne. Elle est considérée comme comportant peu de mortalité ou de morbidité.[1] Afin de préciser ces données nous avons étudié 1000 cas consécutifs de patients opérés dans le service d'urologie de l'hôpital Saint-Luc à Montréal.

## Patients

De 1980 à 1986, 1000 patients furent admis pour traitement d'une pathologie prostatique. L'âge des malades variait de 45 à 97 ans (moyenne de 68.5 ans). Le séjour hospitalier moyen fut de 8.4 jours (de 3 à 61 jours). Au point de vue histologique, 864 patients étaient porteurs d'une pathologie bénigne et 136 patients d'un cancer de la prostate.

## Résultats

Nous avons relevé les complications postopératoires immédiates sur les 1000 dossiers étudiés. Cent-dix-huit ont eu une complication unique alors qu'elles furent multiples chez 21 patients (tableau I). Six patients sont décédés en postopératoire.

Nous allons étudier de façon détaillée notre morbidité qui fut de 14%.

### *Infection urinaire*

L'infection urinaire, prouvée à la culture des urines, a été retrouvée chez 63 patients. Ces cultures furent faites au moment où la sonde urétrale fut retirée et lors de la visite de relance. Les germes les plus fréquemment rencontrés furent l'*Escherichia coli*, l'entérocoque, le *Klebsiella* et le *Staphylococcus epidermidis*. Tous furent traités par antibiothérapie orale et les cultures de contrôle furent négativées.

### *Hémorragie postopératoire*

Trente-cinq patients ont présenté une hémorragie post-prostatectomie.[2] Celle-ci a été immédiate dans 20 cas et retardée dans 15.

**Tableau I** – Complications

| Complication | No. |
|---|---|
| Infection urinaire | 63 |
| Hémorragie | 35 |
| Rétention urinaire | 27 |
| Septicémie | 23 |
| Cardio-vasculaire | 9 |
| Incontinence | 9 |
| Faux trajets | 4 |
| Epididymite | 2 |
| Hyponatrémie de dilution | 2 |
| Pneumonie | 1 |

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*Accepté pour publication le 12 janvier, 1988*

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Le cas le plus tardif a été rencontré au 21e jour postopératoire. Le traitement approprié pour cette condition fut varié; tous les malades ont bien répondu à la thérapie (tableau II).

*Rétention urinaire*

Vingt-sept patients ont présenté une rétention urinaire après l'exérèse de la sonde urétrale.

Chez 21 patients le traitement a consisté à l'emploi d'un parasympathicométique[3] et de la mise en place d'une sonde urétrale pour des périodes variant de 24 à 48 heures. Si le résidu fait après le retrait de la sonde était inférieur à 100 ml le patient était considéré comme ayant répondu au traitement. Quatre patients ont quitté l'hôpital avec une sonde à demeure; ils étaient connus comme souffrant d'une atonie en préopératoire. Deux patients ont dû subir une nouvelle résection transurétrale pour adénome résiduel.

*Septicémie*

Chez les 1000 patients opérés, 23 ont présenté une septicémie avec une hémoculture positive en période postopératoire.

Onze de ces patients avaient une urine stérile à l'admission et les 12 autres étaient porteurs d'une infection urinaire. Cette faible incidence de septicémie s'explique par la préparation préopératoire des malades porteurs ou présumés infectés en préopératoire.[4] En effet, ces derniers ont reçu de l'ampicilline et de la tobramycine intra-veineuse avant l'intervention et durant les jours postopératoires.

**Tableau II** – Traitement

| |
|---|
| Période immédiate |
| Electrocoagulation |
| Ligature chirurgicale des artères prostatiques |
| Transfusion |
| Période éloignée |
| Electrocoagulation |
| Mise en place d'une sonde et irrigation avec ou sans transfusion |

**Tableau III** – Mortalité

| Cause | No. |
|---|---|
| Choc septique | 1 |
| Oedème aigu du poumon | 2 |
| Infarctus aigu du myocarde | 3 |

*Complications d'ordre cardio-vasculaire*

Neuf patients ont présenté des complications cardiaques et vasculaires. L'oedème aigu rencontré chez quatre malades était dû à une surcharge vasculaire post résection transurétrale. Trois patients ont fait un infarctus du myocarde dans les 24 premières heures; ils n'avaient aucune histoire antérieure de maladie cardiaque. Un patient a fait une thrombophlébite nécessitant une anticoagulothérapie, tandis qu'un autre a fait une embolie pulmonaire non mortelle.

*Incontinence urinaire*

Neuf patients ont présenté de l'incontinence urinaire en postopératoire. Quatre manifestaient de l'incontinence d'effort qui a disparu avec le temps et chez cinq autres patients nous avons retrouvé une vessie spastique pour expliquer leurs symptômes qui se sont amendés avec un parasympathicolytique. Aucun patient n'a eu d'incontinence urinaire totale.

*Faux trajets*

Quatre patients ont eu durant les manipulations préopératoires et peropératoires des faux trajets urétraux. Deux de ces patients étaient déjà porteurs d'une cystostomie installée en urgence. Un de ces patients a subi une perforation rectale au moment de l'introduction du résectoscope. Une dérivation par cystostomie fut faite et 2 mois plus tard il subissait une résection transurétrale sans aucune séquelle.

*Hyponatrémie*

Deux patients ont présenté une hyponatrémie de dilution symptomatique. Dans les deux cas les symptômes se sont manifestés dans les 12 heures qui suivirent l'intervention.

*Epididymite*

Seulement deux patients ont présenté une épididymite dans la période postopératoire. Un patient porteur d'une sonde était infecté avant l'intervention.

*Mortalité*

La mortalité postopératoire fut minime (0.6%). La moyenne d'âge des patients décédés étaient de 76 ans. Le choc septique, l'oedème aigu du poumon et l'infarctus furent les principales causes de décès (tableau III).

## Discussion

La mortalité et la morbidité rattachés à la résection transurétrale de la prostate sont faibles. En effet, seulement 14% des patients ont présenté des complications. Près de la moitié, c'est-à-dire 63 patients sur 139, était secondaire à une infection urinaire.

L'hémorragie postopératoire immédiate, bien que rare, peut être corrigée en insistant davantage sur une meilleure hémostase[5] tandis que l'hémorragie à long terme, bien que non prévisible, pourrait être évitée en donnant les conseils d'usage, à savoir éviter les activités sexuelles et les activités physiques.

La septicémie peut être réduite

avec une plus grande rigueur d'asepsie et une identification des malades susceptibles d'être infectés ou porteurs d'infection avant l'intervention de façon à pouvoir leur donner une antibiothérapie préventive au préalable.

La mortalité de 0.6% est basse et elle est comparable aux autres séries connues. Afin de la diminuer il est très important que tous les patients à risque aient une évaluation préopératoire.

L'incontinence postopératoire secondaire à la technique s'est améliorée beaucoup à travers les années. Nous pouvons constater que nous n'avons pas d'incontinence à long terme mais seulement une incontinence d'effort temporaire.

Les sténoses urétrales et les sténoses du col vésical sont des complications beaucoup plus tardives qui surviennent encore malheureusement et pour lesquelles nous n'avons pas trouvé de solution.

## Conclusions

La résection transurétrale de la prostate est une intervention chirurgicale à faible incidence de mortalité et de morbidité. Il est toutefois très important que le malade soit bien préparé et bien évalué.

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## BOOK REVIEWS

*continued from page 412*

reports of each scientist in paper form allows for close scrutiny of the data.

The book is geared more to the research and research-oriented clinical laboratory in the field of growth factors and wound healing. The chapter dealing with platelet-derived wound healing factors in human clinical trials is especially relevant to surgical practice as is the chapter on clinical experience with crude preparation of growth factors and healing of chronic wounds in humans. The authors present state of the art information on alternatives to healing difficult ulcers or wounds for which conventional therapy is slow or ineffective.

The book is easy to read but would have benefited by more editorial comment on how the various scientific presentations relate to clinical pratice. However, this does not deter from the overall aim of the book. It serves as an excellent reference for the research scientist in the area of growth factors and other aspects of wound healing and is a very interesting and clinically relevant reference source for the practising clinical surgeon.


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**PRINCIPLES AND PRACTICE OF RESEARCH. Strategies for Surgical Investigators. Edited by Hans Troidl, Walter O. Spitzer, Bucknam McPeek, David S. Mulder and Martin F. McKneally. 385 pp. Illust. Springer-Verlag, New York. $58.00 (US). ISBN 0-387-16340-9.**

This book on surgical research is divided into six sections. The first section on the rationale of surgical research deals with the historical and philosophical aspects and the role and training of the investigator. The second section concerns itself with practical tools required by the investigator, including such topics as literature review and appraisal, statistics, computers and preparation of grant proposals. The chapter on statistics, entitled "Statistics demystified", is excellent as a review or for the student who has had no exposure to research.

The various aspects of surgical research are covered in the next section. They include animal experimentation, clinical research, multicentre trials and health service research. Three well-written chapters in this section deal with particularly important subjects, not only for the surgical investigator but for every academic surgeon; they discuss the conduct and pitfalls of clinical trials, including multicentre clinical trials, and the evaluation of the diagnostic process in medicine. Practical examples of how to calculate patient size in a clinical trial and how to evaluate diag-

*continued on page 447*

# Acute Pancoast's Syndrome Caused by Fungal Infection

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**Nonmalignant causes of Pancoast's syndrome are extremely rare. The authors report the case of a 32-year-old man, receiving treatment for acute lymphoblastic leukemia, who had a clinical picture resembling that of Pancoast's syndrome. Invasive mucormycosis was diagnosed as the cause of the syndrome at emergency thoracotomy undertaken to control massive hemoptysis. In spite of adequate treatment, the patient died 5 weeks postoperatively of overwhelming sepsis. A review of the literature disclosed only two other similar cases. The authors conclude that the development of Pancoast's syndrome in the immunosuppressed patient should raise suspicion of an invasive fungal infection. A precise early diagnosis may allow successful, specific antifungal therapy to be instituted.**

**Les causes non malignes du syndrome de Pancoast–Tobias sont rares. Les auteurs décrivent le cas d'un homme de 32 ans traité pour leucémie aiguë lymphoblastique, qui présenta un tableau clinique évocateur d'un syndrome de Pancoast–Tobias. Lors d'une thoracotomie pratiquée en urgence pour venir à bout d'une hémoptysie massive, une mucormycose fut diagnostiquée comme cause de ce syndrome. En dépit d'un traitement approprié, le patient décéda 5 semaines plus tard d'une septicémie irrépressible. Une revue de la littérature n'a révélé que deux autres cas similaires. En conclusion, les auteurs indiquent qu'il faut soupçonner une infection fongique invasive quand un syndrome de Pancoast–Tobias apparaît chez un patient dont les fonctions immunitaires sont déprimées. Un diagnostic précis et précoce pourrait permettre le succès d'un traitement antifongique spécifique.**

Pancoast's syndrome, the association of pain in the shoulder and arm, sensorimotor symptoms in the involved upper limb and an ipsilateral Horner's syndrome, is usually caused by a malignant apical lung tumour invading the structures of the thoracic inlet.[1] We present a case of rapidly evolving Pancoast's syndrome that resulted from a fungal infection.

## Case Report

A 32-year-old man presented with a 3-month history of fatigue, night sweats and anorexia. He had become jaundiced 3 weeks earlier and his urine was dark. He had suffered from rheumatic fever as a child.

Physical examination revealed a jaundiced young man with petechiae scattered over most of his body. He had enlarged cervical, axillary and femoral lymph nodes and hepatosplenomegaly. A chest film appeared normal (Fig. 1). Blood smear and bone-marrow examination were diagnostic for acute lymphoblastic leukemia. Induction chemotherapy was with vincristine, prednisone and daunorubicin; the hepatosplenomegaly and lymphadenopathy quickly resolved. Remission as assessed by bone-marrow examination was achieved by 3 weeks.

During the neutropenic period, approximately 5 days after the initiation of chemotherapy, severe constant pain developed in his left shoulder and over the left scapula. He remained afebrile with no cough or hemoptysis. Over the next 4 days, the left shoulder pain increased in severity and radiated down the medial aspect of the left arm; paresthesia developed in the fourth and fifth fingers.

The patient became febrile, so tobramycin, 100 mg intravenously every 8 hours, and cefazolin, 1.5 g every 6 hours, were started. All cultures were sterile but the patient remained febrile and a cough with mild hemoptysis developed. A chest film now revealed left upper lobe consolidation (Fig. 2). Ticarcillin, 3 g intravenously every 4 hours, was substituted for cefazolin. Two days later, approximately 11 days after the initiation of chemotherapy, a left Horner's syndrome developed and a supraclavicular mass that was fluctuant, tender and not erythematous appeared on the left side.

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There was cavitation within the consolidation of the left upper lobe and subcutaneous emphysema in the left side of the neck (Fig. 3). A provisional diagnosis of lung abscess or leukemic infiltration of the left upper lobe was considered.

Fiberoptic flexible bronchoscopy revealed erythema of the left upper lobe bronchus but no evidence of pus or active bleeding. Biopsy specimens and cytologic brushings were obtained, and tissue was cultured. Apart from a light inflammatory exudate and nonspecific bronchitis, there was no evidence of malignant cells, bacteria or fungi. Approximately 8 hours after bronchoscopy, sudden massive hemoptysis developed and the patient suffered a cardiorespiratory arrest. He was resuscitated, but large quantities of arterial blood continued to drain through the endotracheal tube.

On fiberoptic flexible bronchoscopy, the diseased left upper lobe was found to be the source of bleeding. An emergency left thoracotomy, under one-lung ventilation using a Carlen's tube, was then undertaken to remove the diseased lobe, which appeared to be consolidated, necrotic and intimately involved within the apex of the thorax. Mobilization of the diseased necrotic lung from the thoracic inlet was difficult and when the lung was entered the necrotic process was seen to involve the cervical sympathetic chain, the left subclavian artery and the lower part of the brachial plexus. The dissection resulted in extensive bleeding at the apex of the chest wall, apparently from the left subclavian artery; the bleeding was controlled with difficulty using fine vascular sutures. A left upper lobectomy was then completed.

Amphotericin-B therapy was begun; the initial dosage was 5 mg/d intravenously and he received a cumulative dose of 1.57 g. Gram-negative septicemia developed secondary to left lower lobe pneumonia and in spite of vigorous antibiotic and supportive therapy, aortic valve endocarditis and meningitis due to *Serratia marcescens* developed. He died of severe systemic sepsis 5 weeks postoperatively.

## Discussion

The pathological examination revealed mucormycosis. The lung tissue was necrotic and very friable with local thrombus formation in the blood vessels secondary to fungal infection. Numerous fungi were

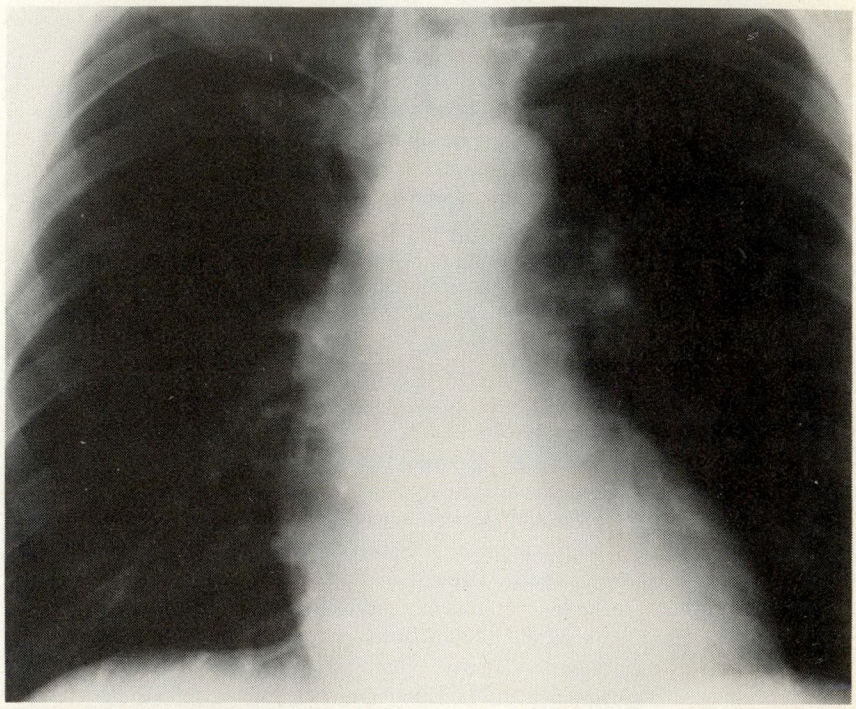

**FIG. 1 — Normal chest film on admission.**

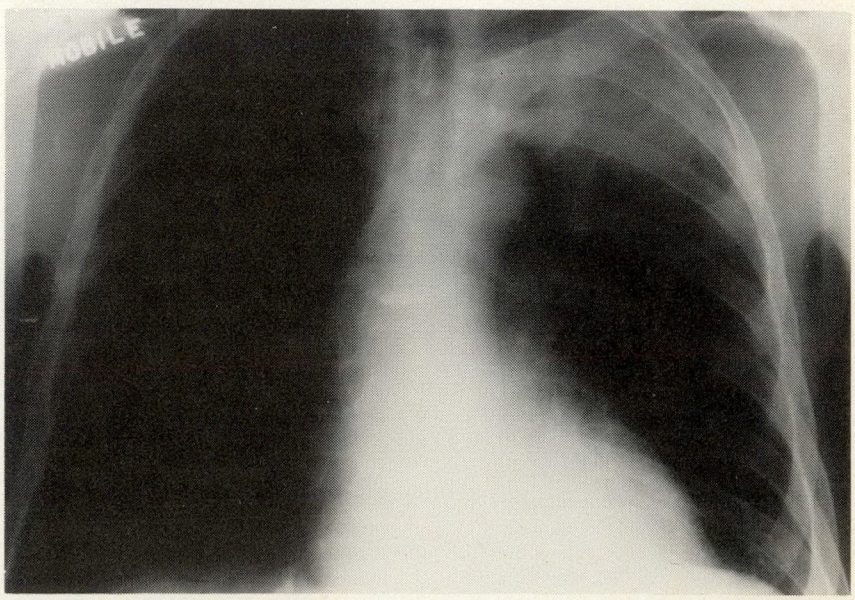

**FIG. 2 — Nine days after induction chemotherapy, film shows consolidation of upper lobe of left lung.**

seen in the lumen of the blood vessels. Examination of the bronchus showed evidence of chronic nonspecific bronchitis only. There was no leukemic infiltrate in the lung tissue or the hilar lymph nodes.

It was our impression that the necrotic disease process in the thoracic inlet of this patient resulted in a bronchovascular fistula between the subclavian artery and the abscess cavity in the left upper lobe; in addition to massive hemoptysis, this fistula was also the source of considerable bleeding that we encountered when we dissected the lung from the chest wall. Involvement of the left brachial plexus and sympathetic chain was responsible for the left arm pain, paresthesia, and Horner's syndrome.

A review of the medical literature revealed two reports[2,3] of a rapidly evolving Pancoast's syndrome occurring in immunosuppressed patients and caused by invasive fungal infection. Our case resembled these in that all three patients were young adults, suffering from hematologic malignant disease in whom an invasive fungal infection occurred during or just after chemotherapy when neutropenia was profound. The picture of well-established Pancoast's syndrome was obvious in these cases within 4 weeks of receiving the induction chemotherapy. The cause of the infection in our case was mucormycosis; *Aspergillus* sp and *Allescheria boydii* were seen in the other cases. Only one patient survived with antifungal therapy;[2] the other[3] died of overwhelming sepsis, as did our patient.

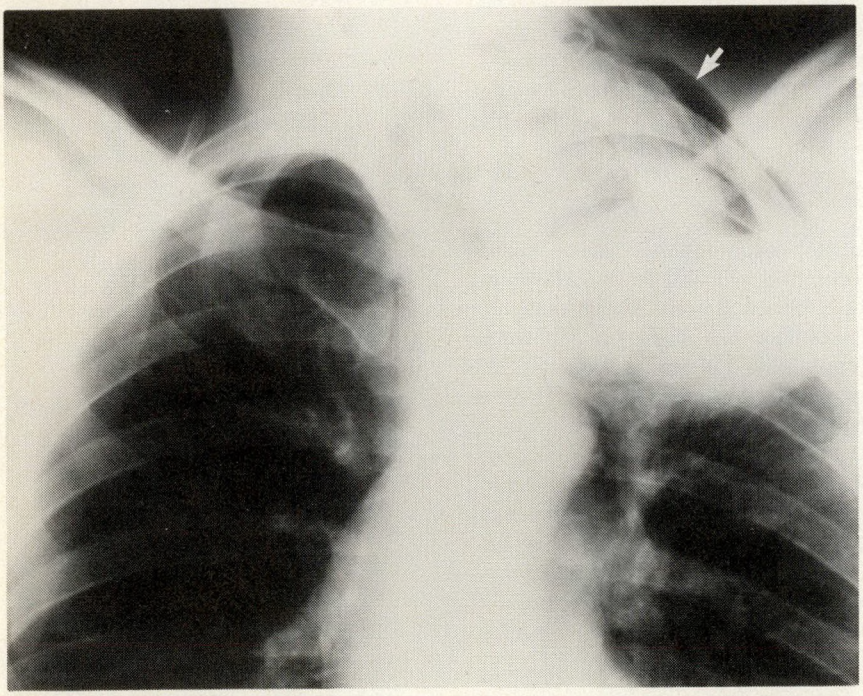

**FIG. 3 — Two days later there is cavitation in area of consolidation with subcutaneous air dissecting into left supraclavicular area (arrow).**

## Conclusions

The development of a rapidly evolving Pancoast's syndrome in an immunosuppressed patient is suggestive of an invasive fungal infection. A precise early diagnosis will allow specific antifungal therapy to be instituted, and treatment of the infection may be successful.

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# Peritoneovenous Shunts — Devices of Last Resort

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**This study examines the usefulness of peritoneovenous shunts through a retrospective review of the charts of 16 patients who received this shunt at the University Hospital in Saskatoon up to May 1987. Fourteen shunts were placed for malignant ascites, 1 for alcoholic cirrhosis and 1 for nephrogenic ascites. All patients had symptoms related to abdominal pressure or dyspnea. Diuretics were most frequently used as initial management, and paracentesis was performed to relieve symptoms in all but one patient. However, a trial of sodium restriction was used in only eight patients, and only five of these trials lasted longer than 1 week. Thus, the adequacy of medical management was questionable. The death of one patient was directly attributable to the shunt, and the deaths of four others were suspected to be sequelae of surgery or shunting. Only five shunts were functioning at the time the patient died. In this study, the majority of the patients received little benefit from the peritoneovenous shunt.**

**Cette étude sur l'utilité des dérivations péritonéo-veineuses fut faite par un examen rétrospectif des dossiers de 16 patients qui reçurent ce type de dérivation jusqu'en mai 1987, à l'Hôpital universitaire de Saskatoon. Quatorze dérivations furent placées pour ascite maligne, 1 pour cirrhose alcoolique et 1 pour ascite néphrogénique. Tous les patients présentaient de symptômes reliés à la pression abdominale ou à la dyspnée. Les diurétiques avaient le plus souvent été utilisés comme traitement initial, et une paracentèse avait été pratiquée pour soulager les symptômes chez tous les patients, sauf un. Toutefois, un apport hyposodique ne fut tenté que chez huit patients seulement, et l'essai dura plus d'une semaine chez seulement cinq d'entre-eux. Il est donc possible que le traitement médical n'ait pas été optimum. Le décès d'un des patients est directement attribuable à la dérivation, et on soupçonne que la mort de quatre autres soit une séquelle de la chirurgie ou de la dérivation. Seulement cinq dérivations étaient perméables au moment du décès des malades. Dans cette étude, la majorité des patients a peu profité d'une dérivation péritonéo-veineuse.**

Since peritoneovenous shunts were introduced in 1974 for the management of ascites, opinions of their benefits and drawbacks have been conflicting. Patient selection is an important factor in determining outcome. Postoperative management may play an important role, and variations in method may account for the variability in the reported results. Even with identical data, different conclusions may be drawn because interpretation of data and perception of "benefit" vary between observers.

Thus, we wished to determine the value of peritoneovenous shunts in the context of our patient population, selection criteria and perioperative management regimens.

## Methods

The charts of all 16 patients who received peritoneovenous shunts at University Hospital, Saskatoon, up to May 1987 were reviewed. Information gleaned from the records included the patient's age, disease, symptoms, management of the ascites before surgery and the surgical procedure used (including type of shunt). The effectiveness of the shunt was determined by comparing preoperative and postoperative patient weights, abdominal girths and symptoms (on postoperative day 7, on discharge and as last reported in the chart or from the family physician's, home or hospital record). Supplemental treatments, patency studies (e.g., Doppler flow) and autopsy findings were noted. Complications postoperatively and patient survival were also considered.

## Findings

Patient age ranged from 21 to 79

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years (mean 55 years) at the time the shunt was placed. In most patients, the disease giving rise to the ascites was malignant (Table I).

The symptoms present before shunt placement included abdominal pressure in 15 and dyspnea in 13 patients. Pleural effusions, present in 6 of the 13, likely contributed to the feeling of dyspnea; 1 of the 13 had congestive heart failure. Heartburn in two patients and back pain in one were less notable symptoms.

Initial medical management of the ascites varied widely. Diuretics were most frequently used (14 patients, Table II). Agents used were hydrochlorothiazide, furosemide and spironolactone. Paracentesis was also a popular therapeutic measure preoperatively. Of the 16 patients, 15 had at least one therapeutic paracentesis (Table III). Only eight patients underwent a trial of sodium restriction to treat their ascites, and this lasted for less than 1 week in three patients, less than 1 month in two and less than 4 months in two others. Fluid restriction was tried in 3 of the 16 patients; 2 were restricted for 5 days and 1 for 29 days.

Until 1982, all shunts used were the LeVeen type (seven patients). Denver shunts were then introduced, and the other nine patients received this shunt.

Eleven patients (69%) had problems after shunting; in all, there were 15 complications (Table IV). In one of the four patients who received prophylactic antibiotics perioperatively, an enterococcal wound infection developed; the same patient also suffered sepsis due to *Peptostreptococcus*.

Autopsy was performed on five patients; three had postoperative complications — congestive heart failure, massive pulmonary embolism and cerebrovascular accident. The congestive heart failure occurred 5 days postoperatively, the pulmonary embolism occurred 2 hours postoperatively in a patient who had been heparinized at operation and the cerebrovascular accident occurred 5 days after operation (the autopsy reported "tumour embolism" as a cause of the stroke). In each of these cases, the complication undoubtedly contributed to the patient's death. When autopsy was not done, it was impossible to prove that the complications were responsible for the patient's death. We noted the time that elapsed between diagnosing the complication and death (Table V).

The length of patient survival with a functioning shunt was determined in patients surviving longer than 1 week (Table VI, Fig. 1). The

**Table I** – Diseases in Patients Who Received a Peritoneovenous Shunt

| Disease | No. of patients |
|---|---|
| Malignant | |
| Adenocarcinoma of | |
| breast | 1 |
| colon | 3 |
| endometrium | 1 |
| gallbladder/common bile duct | 2 |
| ovary | 2 |
| pancreas (suspected) | 2 |
| stomach | 1 |
| Leiomyosarcoma (anaplastic) | 1 |
| Lymphocytic lymphoma | 1 |
| Nonmalignant | |
| Alcoholic cirrhosis | 1 |
| Renal failure/nephrotic ascites | 1 |

**Table II** – Courses of Diuretics Given Preoperatively

| Length of course, wk | No. of patients |
|---|---|
| 0 – 1 | 2 |
| 1 – 2 | 0 |
| 2 – 4 | 4 |
| 4 – 8 | 2 |
| 8 – 16 | 2 |
| > 16 | 4 |

**Table III** – Peritoneal Taps Preoperatively

| No. of taps | No. of patients |
|---|---|
| 1 | 1 |
| 2 | 6 |
| 3 | 4 |
| 4 | 3 |
| > 4 | 1 |

**Table IV** – Complications After Shunt Placement

| Complication | No. of patients (%) |
|---|---|
| Congestive heart failure | 2 (12) |
| Coagulopathy (new)* | |
| Asymptomatic | 3 (20) |
| Symptomatic | 1 (7) |
| Venous thrombosis | 2 (12) |
| Infection | |
| Wound | 1 (6) |
| Sepsis | 1 (6) |
| Ascitic leak | 1 (6) |
| Pulmonary embolism | 1 (6) |
| Cerebrovascular accident | 1 (6) |
| Renal failure† | 1 (6) |
| Shunt displacement | 1 (6) |

*2 patients had coagulopathy preoperatively that was unchanged postoperatively. Coagulation studies were not done on 1 patient.
†Prerenal in nature, especially on days 3 to 7, then resolved.

**Table V** – Survival Related to Complications

| Complication | Postop time of death, d | Time from diagnosis to death, d |
|---|---|---|
| Congestive heart failure | 7 | 2 |
| Congestive heart failure | 10 mo | 10 mo |
| Symptomatic coagulopathy | 30 | 6 |
| Wound infection + sepsis | 30 | 19 |
| Thrombosis of superior vena cava | 3 mo | 83 |
| Thrombosis of superior vena cava? | 31 | 13 |
| Ascitic leak | 22 | 12 |
| Renal failure | 22 | 19 |
| Cerebrovascular accident | 5 wk | 30 |
| Pulmonary embolism | 2 h | – |
| Shunt displacement | –* | –* |

*Alive 3 yr postoperatively.

patient with alcoholic cirrhosis was still alive at the time of writing. The patient with nephrotic ascites, who died 10 months after shunt placement, required repeated paracenteses, starting 5 months after operation. For at least 50% of his remaining life, he received no palliation from the shunt. Figure 2 shows the results obtained with the shunt in patients who had malignant ascites and survived longer than 1 week.

During the first week after shunt placement, most patients received a course of diuretics and, in some cases, sodium restriction. Nine of the 13 who survived longer than 1 week required supplemental treatment (Table VII).

## Discussion

The results of reported studies to date have been comparable to ours. The complications we experienced have also been reported by other groups, although in varying proportions. For example, coagulopathy has been reported in up to 39% of patients (all with nonmalignant ascites)[1] and in as few as 2% (mixed malignant and nonmalignant ascites).[2] The disproportion of malignant cases (14) in our series may account for the relatively low coagulopathy rate, because postoperative coagulopathies have been found to develop less frequently in patients with malignant ascites than in those with cirrhosis.[3] The infection rate in reported studies has ranged from 25%[1] to 2%,[2] and venous thrombosis from 11%[4] to 0%.[1]

Similarly, reports of shunt failure have been inconsistent, but comparisons are difficult because of varying forms in which the data are presented (e.g., cumulative patency, patencies of selected subgroups at a given time, median patency duration). Grischkan and colleagues,[5] for example, reported that 8 of 11 patients studied required either a revision or replacement of the shunt due to malfunction, and Fry and associates[6] found that 55% (33 of 60 patients) had patent shunts at 3 months. In the study of Lund and Moritz,[2] only 10% (5 of 49) shunts failed "in long-term follow-up" (time unspecified).

High death rates have been reported after shunt placement, particularly in patients with underlying malignant disease. One-year survival rates have ranged from 52%[1] to 19%.[2] For malignant ascites, 1-year survival has been reported to vary from 0%[3] to 11%[2] compared with 50%[3] and 54%[2] for patients with cirrhosis. In our study, only three patients (18%) were still alive at 1 year, and this included one of the two patients with nonmalignant ascites.

Patient selection in our institution is based mainly on the referrals of our oncologists and gastroenterologists. The disproportion in the number of patients who had malignant ascites in our study compared with those who had cirrhotic ascites reflects the biases of these specialists. We could not determine from chart review if, or how many, patients referred for shunt insertion were rejected by the surgeons.

**Table VI** – Results After Shunt Placement

| Days after shunt placement | No. of patients alive | No. with functional shunts |
|---|---|---|
| 1 | 15 | 15 |
| 7 | 13 | 11 |
| 14 | 13 | 10 |
| 30 | 9 | 6 |
| 60 | 6 | 6 |
| 90 | 5 | 4 |
| 120 | 3 | 2 |
| 180 | 3 | 1 |
| 360 | 2 | 1 |

**Table VII** – Supplemental Treatments Required in Patients Surviving More Than 1 Week After Shunt Placement

| Treatment | No. of patients |
|---|---|
| Diuretics | 8 |
| Sodium restriction | 4 |
| Fluid restriction | 1 |
| Repeated paracenteses | 2 |

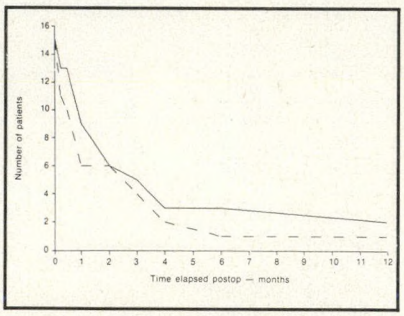


**FIG. 1 — Patient survival and shunt function after placement of peritoneovenous shunt. Solid line = patients alive, dotted line = patients alive and shunt functioning.**

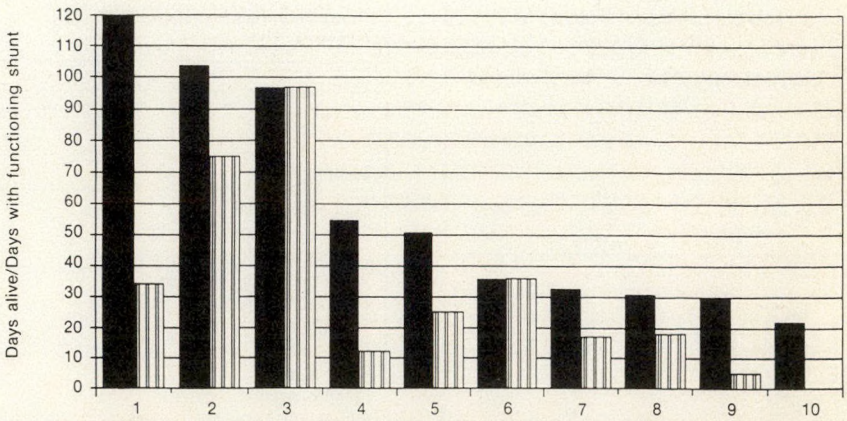


**FIG. 2 — Lifespan and shunt function in 10 patients with malignant ascites who survived longer than 1 week after peritoneovenous shunting. Black bars = total days of life, lined bars = days of shunt function.**

However, it was apparent that several patients receiving shunts had not had optimal medical therapy first, and in many patients the intractability of the ascites was questionable. Sodium restriction, the mainstay of ascites management, was not even tried in two patients and several had only brief courses. Diuretics were used, but again courses in many patients were brief. (Because fluid restriction can precipitate hepatorenal syndrome, it may have been considered undesirable.)

Morbidity and mortality were striking in this small series; 69% (11) of patients had complications. Surgery or the shunt itself likely contributed to the death of at least 38% (six) of patients. Cause and effect could not be proved, even with autopsy, because of the myriad of variables. In all but two patients with complications, death occurred within 30 days of diagnosis.

Overall, patients did not live long after receiving their shunts. Only nine patients were alive 1 month postoperatively, three at 4 months and two at 1 year. Patients who survived longer than 1 week did not necessarily obtain palliation from their shunts for the rest of their lives (Fig. 2). In some cases, palliation was very brief. The majority of patients (69%) required some form of supplemental treatment, including repeated paracentesis, in an attempt to control the ascites.

LeVeen and Denver shunts are not inexpensive. On the other hand, it is an ethical question whether palliation for a day or a month is worth the expense. We found that patients receiving a shunt had a high complication rate, adding to morbidity, and that, generally, they did not live long enough to benefit substantially from the shunt.

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## BOOK REVIEWS

*continued from page 440*

nostic tests are provided. These chapters are among the best in the book.

The fourth section deals with the reporting of research; abstracts, oral presentations and written presentations are considered. There is an excellent chapter on chairing panels, seminars and consensus conferences, areas that are not usually dealt with. All investigators no matter how senior can learn from this chapter.

The fifth section entitled "International perspectives on surgical research" deals with contributions made from different countries. Particularly interesting in this section is a discussion of the problems of developing clinical trials in Japan, given by Drs. Aoki and Hioki and Muto.

The final section of the book is concerned with opportunities and the future of surgical research with a chapter written by Dr. F.D. Moore.

The book has a number of shortcomings. For example, a much more specific and practical discussion of the training of a surgical investigator would enhance the book; it should include such considerations as how to select a research supervisor, how to select an area of interest and whether or not a higher degree should be sought. The important subject of how to write a research paper lacks detail; only one paragraph is devoted to writing a discussion section. There is little or no instruction on the preparation of tables and figures. I also found the section on the role of the surgical investigator somewhat negative. The categorization of surgical investigators into "tightrope walkers, benchmen, or occasional surgeon-investigators" is not in my view likely to attract young people to this endeavour.

These criticisms do not diminish the considerable value of this book and I recommend it for the hospital library as well as the individual surgical laboratory.

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**TOTAL KNEE REVISION ARTHROPLASTY. Edited by W. Norman Scott. 223 pp. Illust. Grune & Stratton, Inc., Orlando, Fla.; Academic Press Canada, Don Mills, Ont., 1987. $88.25. ISBN 0-8089-1864-8.**

This is a timely book in the sense that knee revision procedures are becoming common. Unfortunately, its value is

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# Is Incidental Appendectomy a Safe Practice?

Andrus J. Voitk, MD, MSc, FRCSC; Josiah B. Lowry, MD

**In an attempt to determine the safety of appendectomy performed as an incidental procedure, the authors reviewed 853 operations (458 hysterectomies and 395 cholecystectomies) performed by five surgeons at one hospital between 1981 and 1984 and compared the results in 35% of the patients who underwent incidental appendectomy with those in the remainder. Factors studied were operative time, postoperative stay, postoperative fever and leukocytosis, the need for intravenous fluids, parenteral analgesia and antibiotics, and infectious complications. Most of these variables differed between individual surgeons, but the addition of incidental appendectomy did not significantly alter any variable for an individual surgeon or for the group as a whole. Incidental appendectomy seems to be a safe practice and one that does not alter the outcome of hysterectomy or cholecystectomy but does protect against subsequent appendicitis.**

**Pour tenter d'établir l'innocuité des appendicectomies effectuées accessoirement à une autre opération, les auteurs ont passé en revue 853 opérations (458 hystérectomies et 395 cholécystectomies) pratiquées par cinq chirurgiens d'un hôpital, entre 1981 et 1984. Ils ont comparé les résultats chez 35% de ces patients qui ont subi une appendicectomie accessoire, avec ceux observés chez les autres patients. Les facteurs étudiés comprennent le temps opératoire, la durée du séjour postopératoire, la pyrexie et la leucocytose postopératoires, le besoin de solutés intraveineux, d'analgésiques et d'antibiotiques parentéraux, et les complications infectieuses. On a constaté entre les chirurgiens des différences individuelles quant à la plupart de ces variables, mais l'appendicectomie accessoire n'a modifié aucune des variables pour aucun des chirurgiens ou pour l'ensemble de ceux-ci. L'appendicectomie accessoire semble donc être une pratique sûre qui ne modifie en rien les résultats de l'hystérectomie ou de la cholécystectomie, mais qui protège d'une appendicite subséquente.**

The likelihood of appendicitis developing decreases with age, being approximately 20% for those under 20 years of age, then dropping off abruptly to be only about 1% for those 65 years of age and older.[1] However, the death rate from appendicitis rises with age.[2] The rate of perforation triples after 60 years of age[2] and the likelihood of death from a perforated appendix is three times that of an unperforated appendix.[3] Thus, although the disease is less frequent in the elderly, its effects are much more serious. In order to avoid the risks of appendicitis associated with increasing age, appendectomy performed incidentally at the time of another surgical procedure should be advocated, particularly if it carries no increased risk to the patient.

To determine if incidental appendectomy is associated with undesirable effects, we decided to review the results obtained in a small hospital where incidental appendectomy is common. Cholecystectomy and hysterectomy were standard and frequently performed operations suitable for the study. In this setting, incidental appendectomy carries no monetary reward, as government health insurance allows no additional charge for appendectomy carried out in the course of other surgery.

## Patients and Method

We reviewed the charts of 853 patients who underwent hysterectomy (458 patients) or cholecystectomy (395 patients) at Orillia Soldiers' Memorial Hospital between 1981 and 1984 inclusive. All participating surgeons claimed to use the same three criteria for incidental appendectomy: an uncomplicated primary operation, a stable patient with no contraindication to additional surgery and an original incision providing access to the appendix without need for enlargement. For hysterectomy (Table I), done by two gynecologists and one of the general surgeons, only elective operations on nonpregnant patients

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were included; removal of ovaries, cysts and fallopian tubes were considered part of the procedure, if carried out. Patients who underwent additional procedures, other than appendectomy, were rejected. For cholecystectomy (Table II), performed by three general surgeons, no additional procedures were accepted, but both elective and emergency (patients admitted through the emergency department who had their operation during the same admission) procedures were allowed. The variables studied are listed in Tables III and IV. Because this is a retrospective study, wound infection is recorded only when it was listed as a complication in the discharge summary or progress notes, or when a procedure was noted to be draining pus from the wound. A deep abscess was diagnosed when it was necessary to drain pus from the abdominal cavity. The leukocyte count was not measured in all patients.

Differences between individual surgeons and variables were analysed by the $\chi^2$ test with Yates' correction; a p value of less than 0.05 was considered significant.

## Findings

The overall rate of incidental appendectomy was 35% (299 of 853), 30% (138 of 458) with hysterectomy and 41% (161 of 395) with cholecystectomy. For the five surgeons who performed the procedures, the incidental appendectomy rate varied between 12% and 59% ($p < 0.05$). There was one death in the whole group; a nonogenarian man died of cardiac causes within 48 hours of an emergency cholecystectomy without appendectomy. Comparison of hysterectomy with cholecystectomy showed close similarity between the variables studied. With both operations, no significant difference between appendectomy and no appendectomy was seen with respect to any of the variables.

Of the 395 cholecystectomies 112 (28%) were classified as emergency. They were associated with a significantly lower appendectomy rate than elective cholecystectomies (22% versus 48%, $p < 0.05$) (Table II) and a significantly higher rate of leukocytosis (37% versus 6%, $p < 0.05$), use of intravenous fluids (49% versus 19%, $p < 0.05$) and use of antibiotics (53% versus 15%, $p < 0.05$). But again, within each subgroup of emergency and elective cholecystectomies there was no difference between patients who did or did not have a concomitant appendectomy.

Only infection rates and the incidence of postoperative fever were similar for all surgeons (Table III); all other variables differed significantly from surgeon to surgeon, but no significant difference in any variable could be detected between patients who did and did not undergo concomitant appendectomy.

There were no significant differences in the results of the 853 operations. Specifically, the addition of appendectomy did not increase the length of hospital stay, the incidence of fever or leukocytosis or the need for intravenous therapy, antibiotics or parenteral analgesia. The 10-minute increase in average operative time was not significant. The superficial wound infection rate doubled with appendectomy (6 of 291 versus 6 of 562, $p > 0.05$); deep abscesses occurred in three patients after appendectomy and none in those without. Total complications from infection tripled after appendectomy (2 of 291 versus 6 of 562, $p > 0.05$).

## Discussion

Ten series from this decade, reporting over 1500 patients, did not show a single death attributable to incidental appendectomy, nor did the authors report increased morbidity except with respect to wound infection, where opinions differed. Cruse[4] reported an increased rate of wound infection after cholecystectomy when appendectomy was done incidentally, but Strom and coworkers[5] were unable to confirm this in a prospective randomized study. Despite its apparent safety, incidental appendectomy does not enjoy universal blessing. Morris and col-

**Table I** – Patients Who Underwent Hysterectomy

| Surgeon | With appendectomy | Without appendectomy | Total |
|---|---|---|---|
| 1 | 102 | 201 | 303 |
| 2 | 15 | 106 | 121 |
| 3 | 21 | 13 | 34 |
| Totals | 138 | 320 | 458 |

**Table II** – Patients Who Underwent Cholecystectomy

| Surgeon no. | With appendectomy | | | Without appendectomy | | | Totals | | |
|---|---|---|---|---|---|---|---|---|---|
| | Elective | Emergency | Combined | Elective | Emergency | Combined | Elective | Emergency | Combined |
| 3 | 96 | 17 | 113 | 59 | 21 | 80 | 155 | 38 | 193 |
| 4 | 32 | 3 | 35 | 45 | 14 | 59 | 77 | 17 | 94 |
| 5 | 8 | 5 | 13 | 43 | 52 | 95 | 51 | 57 | 108 |
| Totals | 136 | 25 | 161 | 147 | 87 | 234 | 283 | 112 | 395 |

leagues[6] found the observed increase in wound infection rate following incidental appendectomy to be statistically insignificant, yet they advised against the practice. Nockerts and associates[7] also advised against it, at least in the elderly, as did one-third of the American Surgical Program directors.[8] Among its advocates are Tranmer and colleagues,[9] Shennib and associates[10] and Saade's group.[11]

The variable appendectomy rate (12% to 59%) between individual surgeons in our study suggested that surgeons had used additional selection criteria to those listed or that their application had varied markedly. When we questioned the surgeons, drawing attention to this wide variation, one surgeon admitted to an underlying wish to finish the operation quickly and another had concerns about litigation in the event of mishap. Not surprisingly, the incidental appendectomy rate for both these surgeons was lowest for the group at 12%. If their rates were eliminated, the difference lost its significance.

Clearly, application of the selection criteria favoured the better operative candidates for appendectomy. Thus, the two groups are not necessarily comparable. The patients who had appendectomy would be expected to do well, so it is not surprising that they fared as well as the others.

This study demonstrates that incidental appendectomy, as practised in the clinical setting using the selection criteria outlined, seems safe. To obtain a "true" picture of the contribution of appendectomy, a prospective randomized study would be required with full disclosure to the patient. Such a study would have to eliminate individual variations of practice by having the operation totally standardized; postoperative care would also need to be standardized and provided by someone other than the operating surgeon. Our study suggests that the negative contribution of appendectomy is so small when measured against the concomitant primary operation, that such a complicated study is not warranted.

Most investigators have failed to show any significant difference in patient outcome by the addition of incidental appendectomy, with the possible exception of complications due to infection. In our study, both superficial and deep infection was more frequent after incidental appendectomy. Although this difference was not significant, a study with greater numbers might show this to be a "true" observation. The potential risk of infection must be weighed against the potential gain when deciding to carry out appendectomy at the time of another procedure.

The most objective variable studied was postoperative fever. Body temperature was recorded every day for all patients by a reliable and disinterested observer (the nurse). There was no significant difference in the occurrence of fever between any of the patients. Despite marked individual variation in other areas, fever rates did not vary significantly between individual surgeons. Leukocytosis was a variable that might be expected to be objective. However, since it was not measured on all patients, the difference probably reflects the degree to which individual surgeons requested this measurement. A difference in operative time would be expected, and postoperative stay also seemed to vary with the individual surgeon's routine.

**Table III** – Maximal Surgeon Variation

| Variable | Average values: All surgeons | Lowest individual | Highest individual | p value* |
|---|---|---|---|---|
| Incidental appendectomy, % | 34 | 12 | 59 | < 0.05 |
| Average operative time, min | 74 | 62 | 101 | < 0.05 |
| Average postoperative stay, d | 6.3 | 4.7 | 8.1 | < 0.05 |
| Fever, % | 42 | 25 | 53 | > 0.05 |
| Leukocytosis, % | 12 | 0 | 25 | < 0.05 |
| Intravenous fluids > 24 h postop, % | 15 | 7 | 47 | < 0.05 |
| Parenteral analgesia > 48 h postop, % | 23 | 5 | 29 | < 0.05 |
| Antibiotics > 24 h postop, % | 18 | 5 | 27 | < 0.05 |
| Total infection rate (wound and deep abscess), % | 2 | 0 | 5 | > 0.05 |

*Difference between highest and lowest.

**Table IV** – Comparison of Average Values for All Patients

| Variable | Average values: All patients, n = 853 | With appendectomy, n = 291 | Without appendectomy, n = 562 | p value |
|---|---|---|---|---|
| Incidental appendectomy, % | 34 | 100 | 0 | – |
| Average operative time, min | 74 | 81 | 71 | > 0.05 |
| Average postoperative stay, d | 6.3 | 6.3 | 6.3 | > 0.05 |
| Fever, % | 42 | 37 | 45 | > 0.05 |
| Leukocytosis, % | 12 | 9 | 13 | > 0.05 |
| Intravenous fluids > 24 h postop, % | 15 | 15 | 15 | > 0.05 |
| Parenteral analgesia > 48 h postop, % | 23 | 22 | 23 | > 0.05 |
| Antibiotics > 24 h postop, % | 18 | 15 | 19 | > 0.05 |
| Wound infection rate, % | 1 | 2 | 1 | > 0.05 |
| Deep abscess incidence, % | 0.4 | 1 | 0 | > 0.05 |
| Total infection rate (wound and abscess), % | 2 | 3 | 1 | > 0.05 |

Similarly, use of intravenous fluids, antibiotics and parenteral analgesia seemed more a function of individual practice than operative procedure or patient need.

Awareness of individual practice is important in clinical studies. For example, although the appendectomy rate for each surgeon performing cholecystectomies was less in the emergency situation, the differences were not significant. Yet, when all emergency cholecystectomies were compared with all elective ones, the lower appendectomy rate in the emergency situation was significant. This can be explained by the fact that the surgeon with the lowest appendectomy rate contributed over half the emergency cholecystectomies, whereas the surgeon with the highest appendectomy rate contributed over half of the elective cholecystectomies.

Regardless of significant differences observed between individual surgeons, the addition of appendectomy to hysterectomy or cholecystectomy in our study made no significant difference to any measured variable for any surgeon and thus had no significant effect on patient outcome. It appears to be an effective and safe prophylaxis against appendicitis, its application seeming to depend on individual judgement and training. The only caveat is a potential increase in infection. Despite its apparent safety, increasing litigation in this country may make this practice less appealing in the future.

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## BOOK REVIEWS

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limited, having been written by the "cement is best, now and forever" school of knee replacement.

The quality of the chapters varies. Some, such as Dohr's on the mechanisms of failure of prostheses, are quite good. Some contain information that, while technically correct, is downright dangerous. Craig, a plastic surgeon, has written a good chapter on skin grafting around the knee, but states that "a lateral or medial parapatellar incision, even when very long, can safely co-exist with the midline approach to the knee". Early in my experience I tried this and in two patients lost the skin off the front of the knees. I believe that the majority of surgeons doing this procedure would advise using the old incision, even if the placement is suboptimal.

Another curious chapter deals with massive defects in the femur on removing ingrowth-type prosthetic components. The authors' technique seems to be to lock on a large slap hammer and batter out the component. If the femoral component is well fixed, it is not surprising that they pull out a lot of bone, indeed it is surprising that they don't pull off the whole distal femur. Fortunately, in a later chapter, other authors indicate the appropriate way to remove these implants.

There is no mention in the book of stress shielding or stress relief osteoporosis which is an important factor in knee revisions. Takedown of a knee fusion is mentioned briefly, and it is stated that a constrained prosthesis is always required. This is definitely not the case.

Hinges and fixed axis prostheses are condemned, the preferred alternatives being a total condylar III or a custom prosthesis. Custom implants cost at least $5000. so they really have no market outside the United States. The only noncustom prosthesis with huge stems is the Guepar II hinge. If the ligaments do not help to stabilize the knee, then stability comes from the prosthetic components. The interface between bone and implant therefore sees roughly the same loads whether or not the implant is a true hinge or an unlinked hinge such as the total condylar III. This would seem reasonably easy to understand, but the authors seem to have a conceptual block on this subject. In spite of this book, I recommend that any surgeon doing a knee revision have a Guepar II hinge on the back table, just in case it is needed.

The target audience for this book is not obvious, except perhaps the orthopedic residents in New York and Boston.

Hugh U. Cameron, MB, ChB, FRCSC

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# Doctor or Mister (the Correct Appellation of British Surgeons)

Philip Eibel, MD, FRCSC

**The form of address for British surgeons — "Mister" instead of "Doctor" — has mystified other members of the medical profession for years. The author attempts to show that the designation "Mister" is neither an affectation nor a denigration but a natural consequence of the history of British barbery, barber-surgery and ultimately surgery, resulting from the advice and tutelage of King Henry VIII and Parliament.**

**Le titre donné aux chirurgiens britanniques, "Monsieur" plutôt que "Docteur", continue, depuis des années, à laisser perplexes les autres membres de la profession médicale. L'auteur tente de démontrer que la désignation "Mister" n'est pas utilisée par affectation et qu'elle n'a pas de connotation péjorative, mais qu'elle découle plutôt de l'Histoire des barbiers, barbiers-chirurgiens et, ultimement, chirurgiens britanniques, conséquence de l'avis et de la tutelle du roi Henri VIII et du Parlement.**

Surgeons from the United States and Canada visiting hospitals in Great Britain find it difficult to understand why their British colleagues are referred to as "Mister" and not "Doctor". After many arduous years of study to acquire the much-coveted fellowship in surgery it can be disconcerting to address similarly qualified British colleagues by the seemingly lowly title of "Mister". Actually, "Mister" is not a denigration, and British surgeons may even be offended if addressed as "Doctor". But why the difference from almost universal practice?

Despite personal communication with the Royal College of Physicians and Surgeons of England (January 1987) and with the Wellcome Institute for the History of Medicine (March 1987), I could not find documentation of the origin of this British custom. This appellation may have arisen from events that began when surgery and barbery were first recognized as arts and vocations in Britain.

After the dissolution of the Roman Empire, the little surgery that continued to be carried out in Europe was to be found only in monasteries,[1] where monks and their assistants, the barbers, carried on the almost forgotten art of surgery bequeathed to them by the Greeks and Romans. In addition to clipping hair and shaving, barbers helped the monks with more complicated tasks such as blood-letting, believed to be the origin of the colours on the barber's pole — red stripes representing blood and white, the bandages used for stanching.

In 1123 AD, Pope Calistas II decreed that monks must not shed blood. This ruling gave an extraordinary boost to the barbers who now performed, in addition to their regular chores, more complicated procedures such as tooth-pulling, blood-letting and treatment of fractures. Because of this, barbers now became known as barber-surgeons and, in keeping with the Pope's orders, monks ministered only to the souls of patients; their guiding principle was *Ecclesia abhorret a sanguine* (the Church abhors the shedding of blood).[2] Even so, they continued for a long time, as observers and advisers, to impart their superior knowledge of surgery.

Originating at about the same time as the barber-surgeons was a more exalted but less numerous group, the "pure" surgeons. They were more skilled than the barbers but were likewise unlettered, manual workers. They were apprenticed, not university trained and, unlike physicians, could not speak Latin. Because they had no university degree, they could not style themselves as "Doctors".

In 1423, an attempt was made to improve the practice of medicine by forming a conjoint college of the university trained physicians and apprentice-trained surgeons;[3] the barber-surgeons were excluded. The association survived only 1 year, probably because of the opposition of barber-surgeons who were afraid

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of losing their control of the field of surgery, or perhaps because of the tendency of physicians to look down upon the surgeons.[3]

In 1493, the surgeons decided to enter into a working agreement with the barber-surgeons regarding their respective spheres of influence in the practice of surgery and barbery.[4] However, encroachment on each other's territory led to bickering. Surgeons were not above hair-clipping and barbers would occasionally dabble in surgery.

In 1540, Henry VIII, by act of Parliament, completed and extended the particulars, uniting the two groups under the name of the "Masters, Governors, of the Mystery and Commonalty of Barbers and Surgery of London".[5] Henceforth, by royal edict, the barbers could engage only in barbery and the drawing of teeth; surgeons had to abstain from cutting hair and shaving. This association was maintained for over two centuries, until 1745.

The advantages of union were mutual. The surgeons, who were a more select body though fewer in number, helped to raise the prestige of the barber-surgeons. The latter group, more numerous and more affluent, had their own hall (the Barbers' Hall), where lectures were given in anatomy and surgery,[4,6] thus perfecting and advancing the art of surgery.

King Henry VIII gave each member of the newly formed group the right to be addressed as "Master." In time, according to the *New English Dictionary on Historical Principles*, "Master" was pronounced "Mister".[7] Skeat, in his *Etymological Dictionary of the English Language*[8] adds that "Mister" is a back formation from "Mistress", the feminine for "Master". It seems, therefore, that when a British surgeon is addressed as "Mister" he is actually being honoured — in reality he is being called "Master".

The union of barbers and surgeons lasted until 1745 when the latter petitioned Parliament to effect a separation.

From this date, although they had been instrumental in reviving and spreading the knowledge of anatomy and surgery, the place of barber-surgeons was gradually taken over by surgeons. The barbers and barber-surgeons became an honourable, benevolent organization to which leading surgeons of England are now proud to belong. They hold bimonthly Court dinners and maintain the traditions of the old barber-surgeons. Only one-third of them are members of the medical profession. They are now a charitable foundation, dispensing bursaries for deserving boys and girls and pensions to retired barbers and to nurses in need. They provide study grants for the history of surgery. *The Cutting Edge*,[9] a detailed history of the early surgeons, was written in 1974 by a non-medical member, Theodore R. Beck, who is an architect and antiquarian.

The original beautiful Barbers' Hall was destroyed by incendiary bombs in 1940. It contained many treasures, including the painting by Holbein of King Henry VIII and the barber-surgeons. It was rebuilt and was reopened in 1969 by Her Majesty the Queen Mother who gracefully accepted honorary membership in the Worshipful Company of Barbers.[10]

With these romantic traditions stemming from a time when surgery in Britain was in its infancy, it is easy to see why British surgeons adhere tenaciously to the salutation of "Mister".

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## BOOKS RECEIVED

*continued from page 403*

**Progess in Clinical and Biological Research, Volume 277. Advances in Urologic Oncology.** Edited by Nasser Javadpour and Gerald P. Murphy. 150 pp. Illust. Alan R. Liss, Inc., New York, 1988. $48.00 (US). ISBN 0-8451-5127-4.

**Reconstruction Surgery and Traumatology, Volume 20. Gentamicin-PMMA-Chains in Bone and Soft-Tissue Infections.** Edited by H. Eberle. 122 pp. Illust. S. Karger AG, Basel, 1988. $73.50 (US). ISBN 3-8055-4603-3.

**Revascularization for the Ischemic Brain.** Edited by Donald L. Erickson. 294 pp. Illust. Futura Publishing Co., Inc., Mount Kisco, New York, 1988. $45.00 (US). ISBN 0-87993-320-8.

**Vascular and Multi-Infarct Dementia.** Edited by John Stirling Meyer, Helmut Lechner, John Marshall and James F. Toole. 276 pp. Illust. Futura Publishing Co., Inc., Mount Kisco, New York, 1988. $39.00 (US). ISBN 0-87993-323-2.

## ADVERTISERS' INDEX



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**BIOGRAPHY:** – Material for biography of the late Professor J. C. Grant required. Personal memoirs, anecdotes, photographs, welcome. Information treated with discretion and material returned promptly. Reply to: **Dr. Clayton Robinson, 808 - 750 W Broadway, Vancouver, BC V5Z 1H7.** –S88-39

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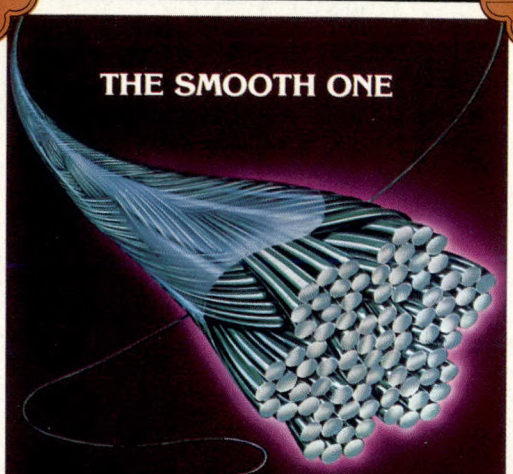

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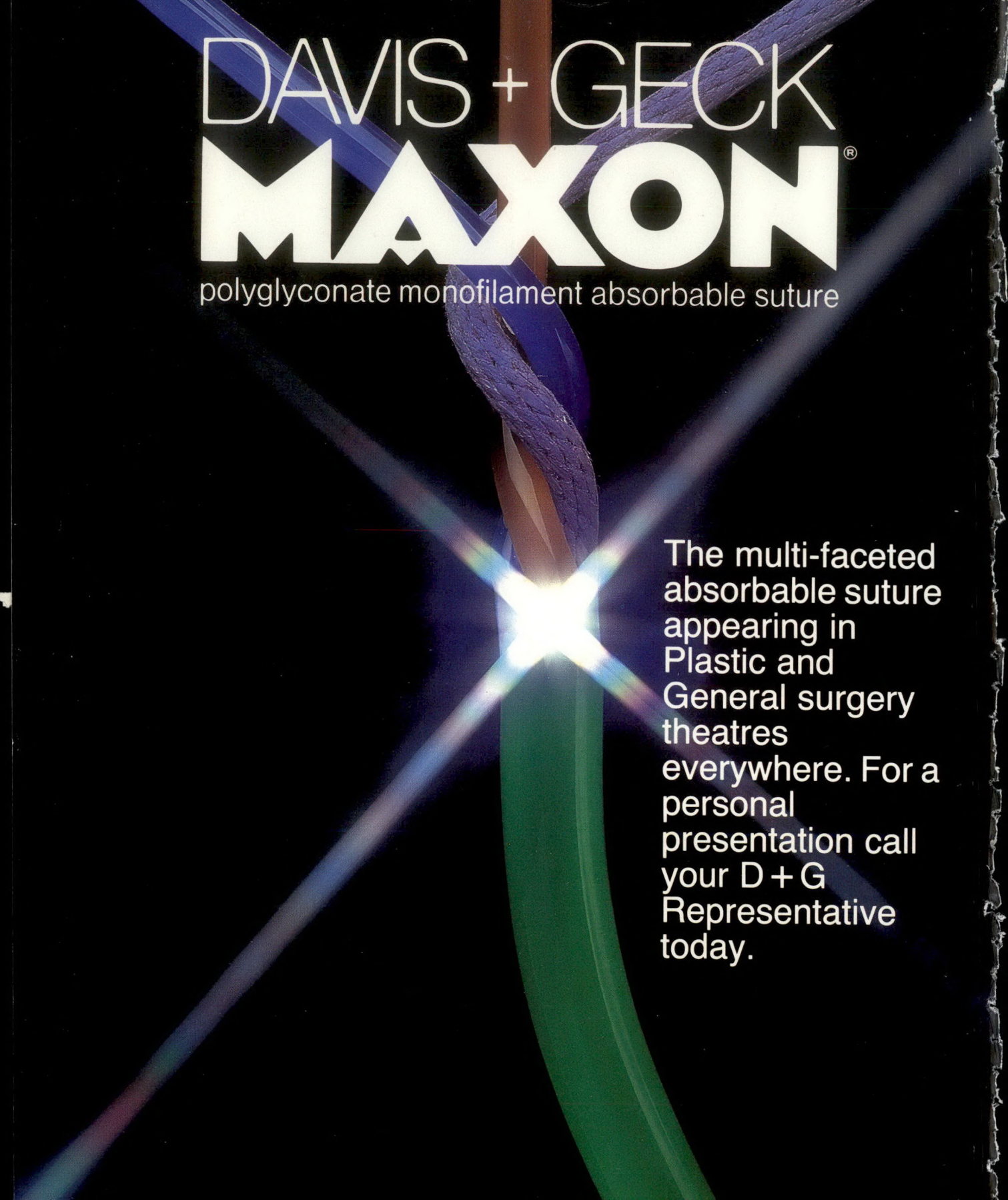
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